Paid Circulation, 35,684

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 253 SEPTEMBER 1, 1955 NUMBER 9

Original Articles

Exercise in the Disposition of Dietary Calories: Regulation of Serum Lipoprotein and Cholesterol Levels in Human Subjects . . 349
George V. Mann, Katherine Teel, Olive Hayes, Ann McNally and Dorothy Bruno

Pancreatitis: Observations on 131 Patients . . 355
James J. O'Brien and Theodore R. Thayer

Hyponatremia in the Urologic Patient . . . 360
Edward L. Peirson

Multiple Benign Chronic Gastric Ulcers: Report of Two Cases Each with Three Simultaneous Ulcers 363
Thomas A. Johnson and Herbert L. Hawthorne

Medical Progress

The Human Hemoglobins in Health and Disease (To be concluded) 365
Amoz I. Chernoff

Medical Intelligence

Chronic Subdural Hematoma of the Spinal Cord: Report of a Case 374
J. Paul Rader

Doctors Afield: François Rabelais 376
Richard Warren

Case Records of the Massachusetts General Hospital

. 379

Editorials

Reversal of Tuberculin Reactivity 388

AMA "Seal of Acceptance" Abandoned . . . 389

Maternal and Infant Health 390

Polio Money Runs Short 390

Massachusetts Medical Society 390
Massachusetts Department of Public Health . . 391
Correspondence 392
Book Reviews 392
Books Received 393
Notices 394

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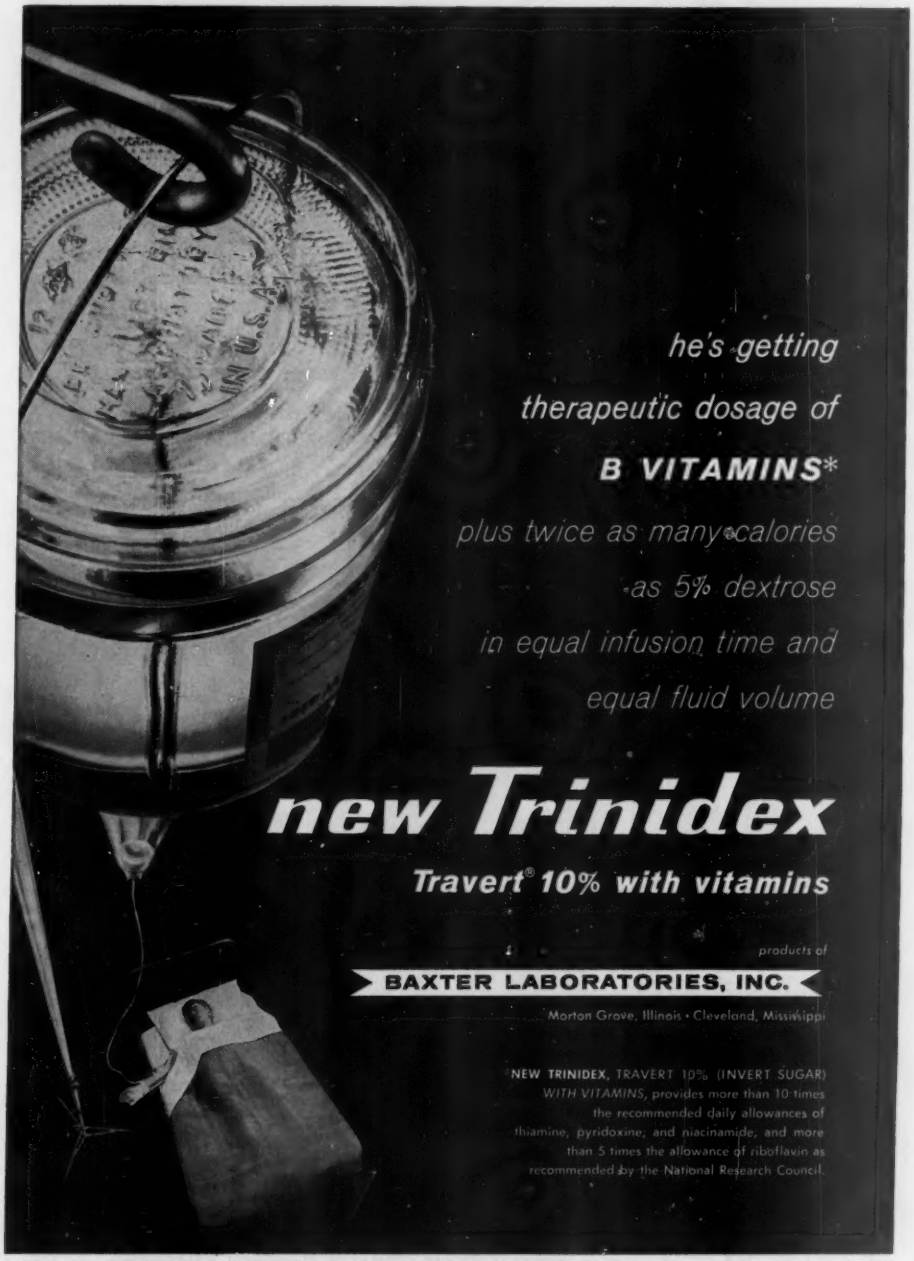
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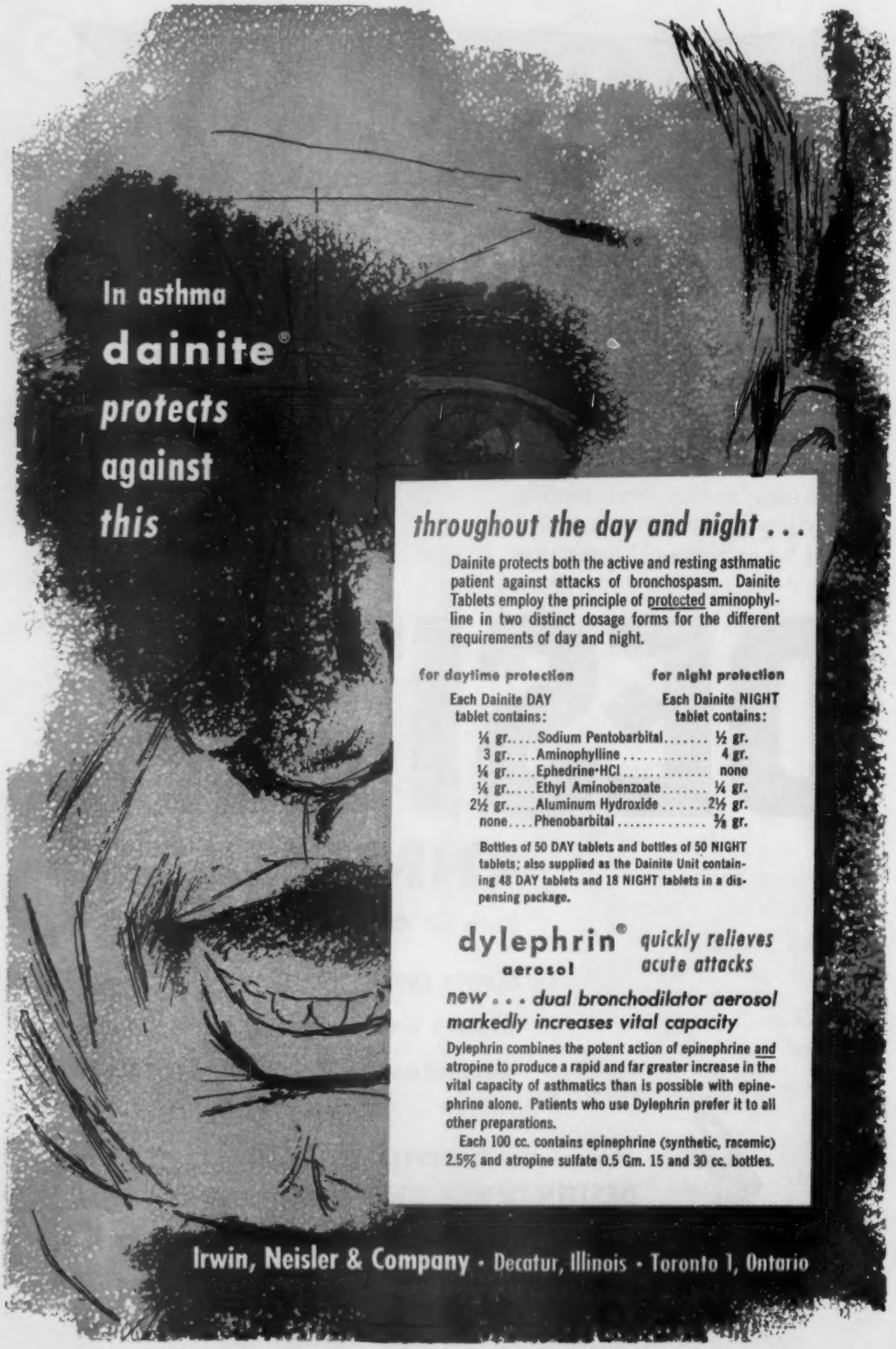

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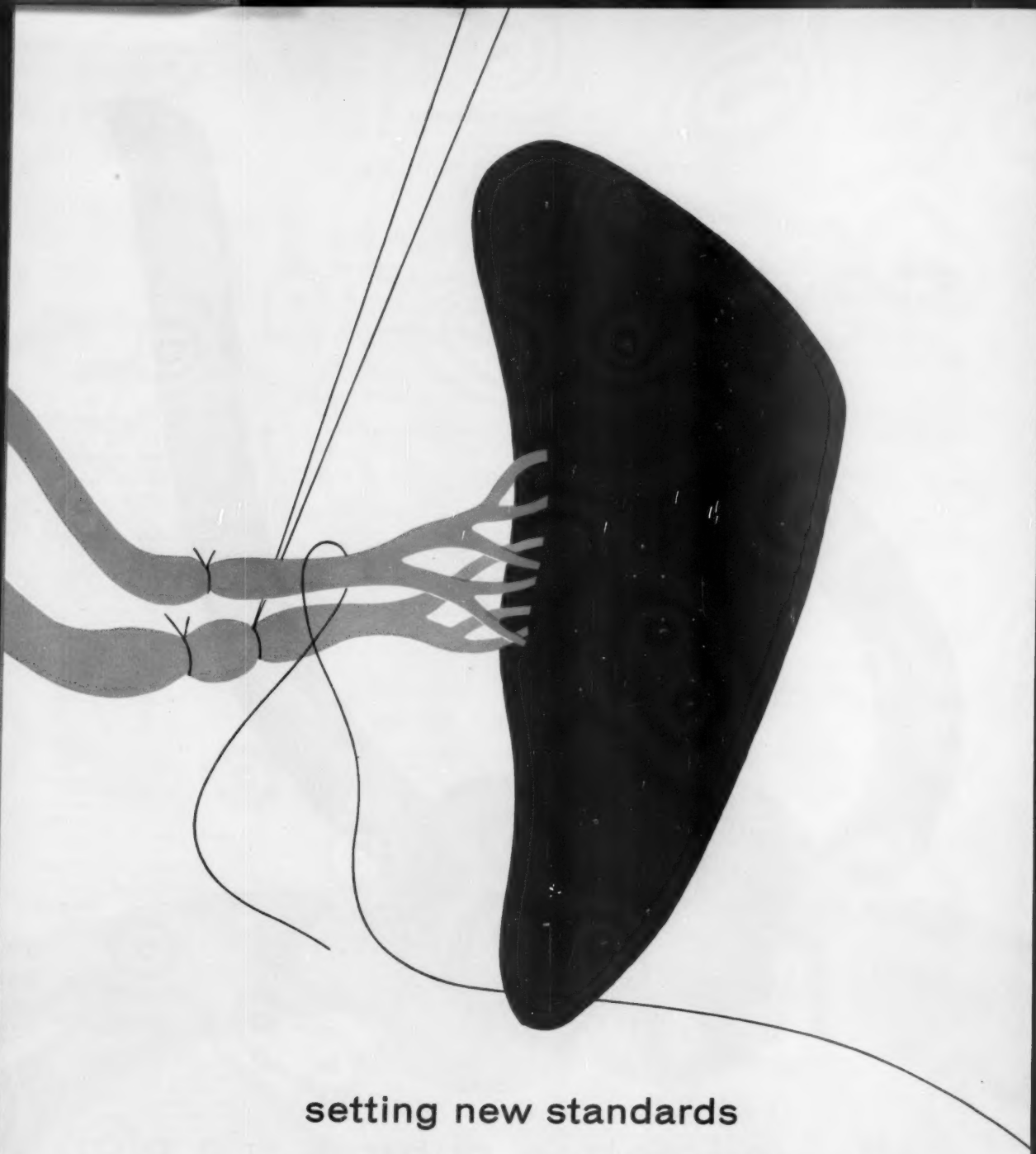

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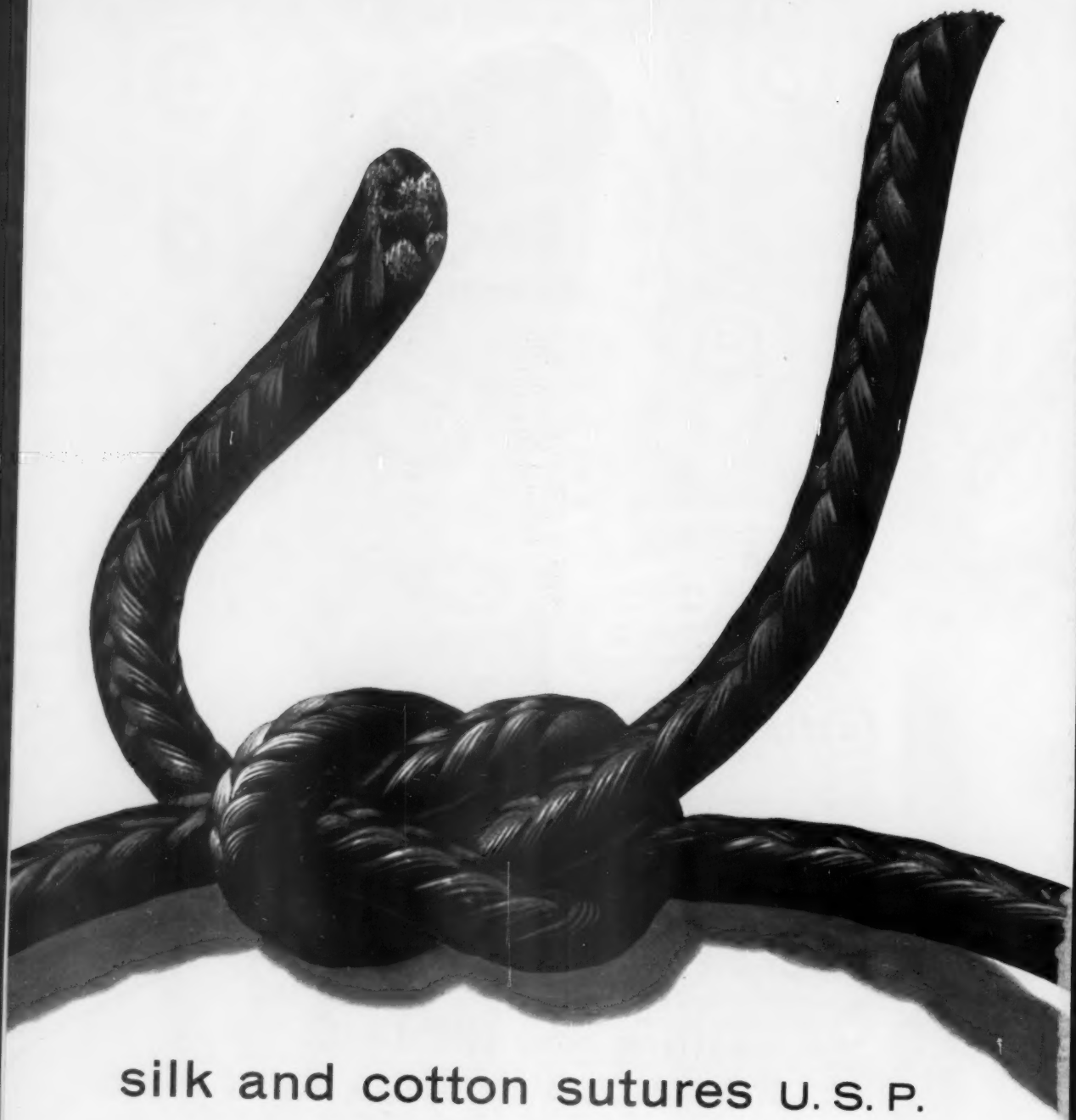

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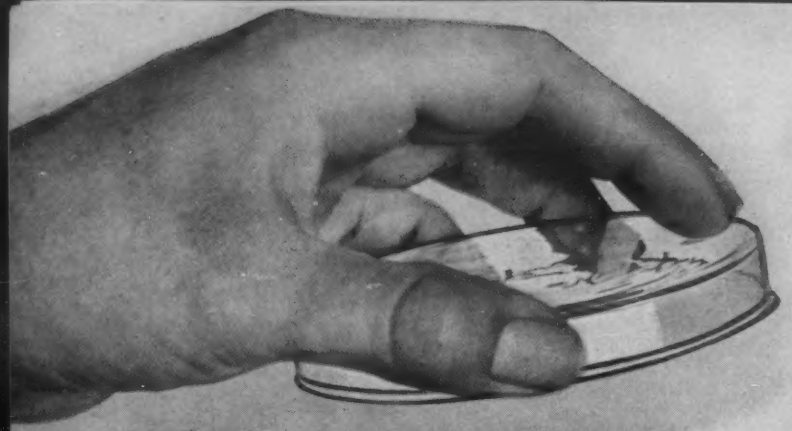

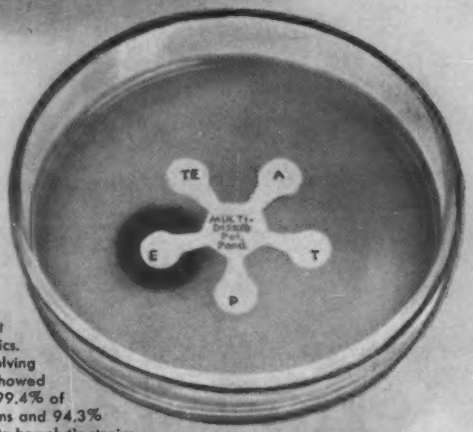

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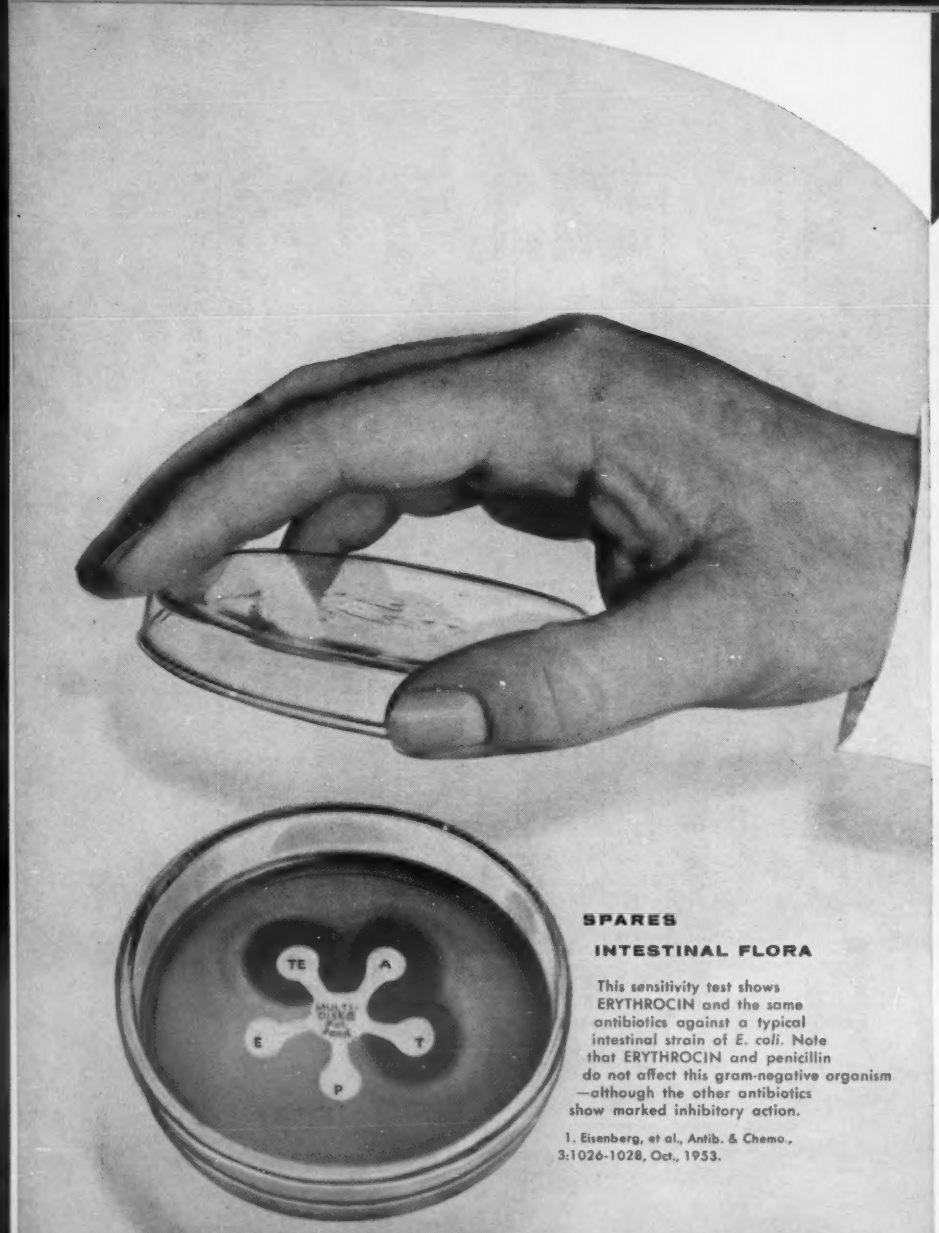

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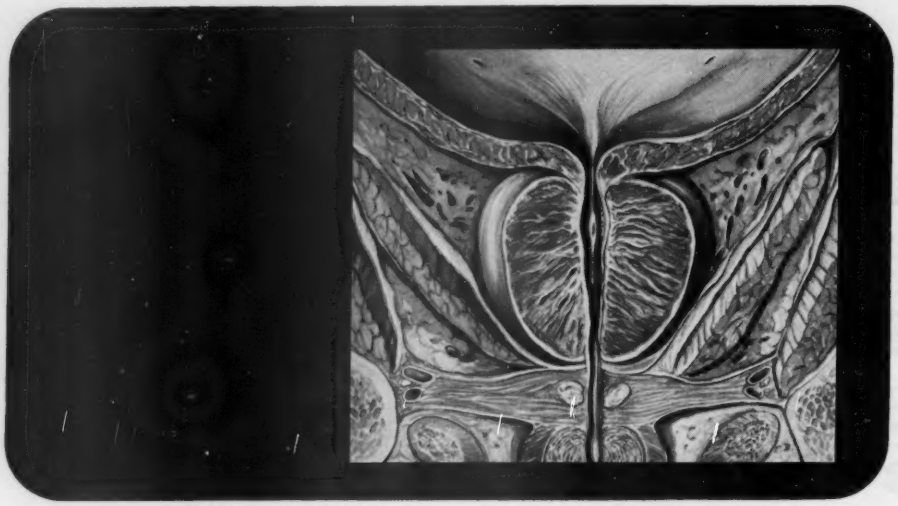

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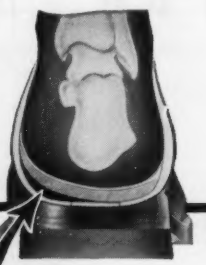

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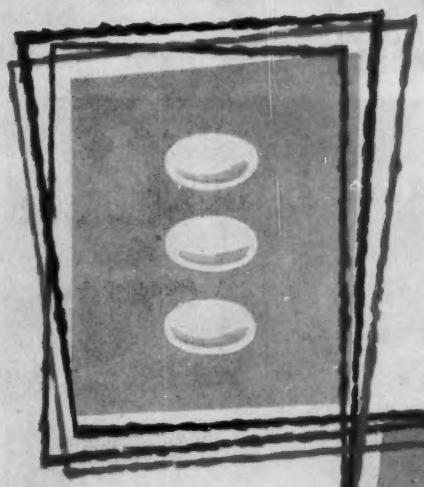

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Volume 253 SEPTEMBER 1, 1955 Number 9

EXERCISE IN THE DISPOSITION OF DIETARY CALORIES*

Regulation of Serum Lipoprotein and Cholesterol Levels in Human Subjects

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ANN MCNALLY§ AND DOROTHY BRUNO§

BOSTON

THE evidence relating the level of the serum lipids to the etiology of human atherosclerosis is indirect.[1] The association of atherosclerosis or its clinical consequences with a record of persistent hypercholesteremia has been observed on many occasions and in both natural and experimental conditions. The relation exists in several species although the degree of association appears to be species specific.[2,3] The development of refined biophysical methods for the characterization of serum lipids has not greatly clarified this relation of serum lipids to disease although the new methods have emphasized a lack of correlation between the serum cholesterol and lipoprotein quantities in human subjects that was unexpected in view of the biochemical similarities of the two and the close correlations found in subhuman animals that have been studied both before and after hypercholesterolemia was induced.[4,5]

A study of the serum lipid levels of Central American human subjects subsisting on vegetarian diets revealed an unexpected dissociation of the serum beta-lipoprotein and cholesterol levels.[6] Those subjects showed low and almost constant cholesterol levels at all adult ages. The levels, which were near 150 mg. per 100 cc. for both sexes of that adult population, are characteristic of North American children. In contrast, the serum beta-lipoprotein levels in the Central American subjects were similar to those of the North American subjects when compared according to age and sex. It became of interest to examine the proposition that some characteristic of the environment of the Central Americans might account for these observations. There were two conspicuous differences between the study groups. The first was that the Central Americans were found to eat much less fat than the North Americans. Although it has been shown that limitation of dietary fat often leads to a reduction of the serum cholesterol and serum beta-lipoprotein levels, the studies offer no evidence that this treatment will selectively lower the cholesterol level, leaving the beta-lipoproteins unchanged or even increased as would be necessary to explain the Central American findings.[7] The second difference was that the studies in Central America indicated that although those subjects were thinner than age-matched and sex-matched North Americans, the Central Americans consumed more food daily in relation to body size. These facts could only mean that high energy expenditures by the Central Americans must account for the weight differences. This conclusion was consonant with the vigorous activity required of individuals in that agrarian culture. We were thus led to consider that there might be some salutary effect of muscular exercise on the regulation of the serum lipids that would selectively keep the serum cholesterol level low. An effect analogous and perhaps related to the favorable effect of exercise upon the carbohydrate metabolism of diabetic subjects was envisioned.[8] A corollary to this explanation would be an opposite effect on the cholesterol level resulting from the diversion of excess food calories to fat deposition, a process that is characteristic of many North American adults and would lead to an elevation of the serum cholesterol level.

It has been shown by Gofman and Jones[9] and by Walker[10] with the data of Dawber et al.[11] that a significant relation exists between the degree of obesity and the level of either the serum cholesterol or the beta-lipoprotein. Our experience with another North American population agrees with these findings.[12] We have also shown[13] that a period of weight

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This work was carried out during the tenure of an established investigatorship of the American Heart Association.

This work was supported by grants-in-aid from the National Heart Institute (NO. H-932-C), National Institutes of Health, Public Health Service, Bethesda, Maryland; the National Livestock and Meat Board, Chicago, Illinois; the American Meat Institute, Chicago, Illinois; and the Albert and Mary Lasker Foundation, New York City.

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loss in human subjects will result in a reduction of the levels of serum lipoproteins and cholesterol but only if these were initially elevated. Conversely, we showed that a short period of rapid weight gain accomplished on a low-fat diet increased both those serum lipid components. In the first of those experiments the dietary lipids were not always constant so that the serum effects could not be related to a single cause. In the second experiment the trial period was short, and only 2 subjects were studied.

An experiment has been designed to evaluate this hypothesis: the magnitude of the total caloric turnover in human subjects controls the serum lipoprotein levels, and the disposition of the calories supplied in the diet controls the serum cholesterol level; when an excess of food calories is converted to body fat, the serum cholesterol level is high, and when a caloric balance or deficit is present, the serum cholesterol level is low.

This hypothesis would adequately explain the Central American observations referred to above, as well as the observations of the relation of overweight and serum lipids in North Americans and the effects of weight reduction and rapid weight gain on the serum lipids. It seemed to be consistent with the effects of treatment of patients with thyroid hormone demonstrated by Freedburg, Kurland and Mann.[14] The hypothesis was not compatible with the finding of low levels of beta-lipoproteins in children[15] and small mammals[4,5] with high energy exchanges.

Methods

The experimental problem was one of varying independently the total caloric turnover and the disposition of excessive calories in adult human subjects. Since the experimental conditions were to be rigorous and the expected serum lipid changes were increases, it appeared desirable to use vigorous young male subjects. Four medical students were engaged to participate in an experiment of ten weeks' duration. The subjects were paid a per-diem wage in addition to their food, and this was the principal initial motivation of 3 of the men. The fourth, although also paid, was interested in the outcome of the experiment. Payment depended on completion of all the conditions of the experimental design.

The men were fed at a research diet table during the entire experiment.* Food was prepared in the hospital kitchen and served by research dietitians who measured the intakes of each item. The subjects were observed for the first week (Period A) under these conditions on an ad-libitum food intake with their usual scholastic activity and while maintaining their body weights at a nearly constant level. From these dietary measurements the intakes of fat and total calories were computed† and averaged for each subject. In the second period (Period B), which was of four weeks' duration, the caloric intake was doubled whereas the fat intake was kept constant at the control level and the subjects were required to maintain their body weights within 5 pounds of the mean weight during the control period by strenuous daily exercise. This was the period of high energy expenditure. In the third period (Period C), of three weeks' duration, the subjects returned to the control level of energy expenditure, but the high-calorie and constant fat intake continued, thus permitting the deposition of body fat. In the fourth and final period (Period D), of two weeks' duration, the subjects were restricted in food calories, the exercise and dietary fat remaining constant, to remove the fat deposited in Period C.

The large food intakes were reached by a stepwise increase over forty-eight hours at the beginning of the second period of the experiment, to give the subjects time to adapt to this great dietary change. During the seven weeks of high energy intake the subjects ate three major meals under observation at the research table and in addition took supplementary feedings consisting principally of measured amounts of candy bars, marshmallows and soft drinks. These supplementary meals furnished 25 to 30 per cent of the total daily calories.

The high energy expenditure was accomplished by a rigorous schedule of daily physical training. During Period B the subjects spent three hours every day in vigorous physical activity in a gymnasium. Swimming, basketball and sprinting proved the most useful activities. These activities were supplemented as necessary by cycling and outdoor running.

On six occasions during the experiment the subjects were weighed in air and in water according to the general procedure of Behnke, Osserman and Welham[17] for the estimation of body volume, and from these data computations of body composition were made. The pulmonary residual air volumes were measured on four of these occasions by the closed-circuit, helium-dilution technic[18]‡ and residual air volumes were interpolated for the other two sets of density computations. This residual air procedure has been shown to be reliable within 150 cc. The underwater weighings were made in a tranquil swimming pool at 27°C. and were accurate to 60 gm. The density computations were corrected to absolute densities at 27°C. The percentages of total body fat were derived from the tables of Pace and Rathbun.[19] The proportion of obese tissue (G) and fat (F) that relate observed body density to the relative fatness of 25 normal men of this age were computed with the equations of Keys and Brožek.[20]

Blood was drawn in the postabsorptive state at weekly intervals during the experiment, and the serum was used for the measurement of beta-lipo-

*We are indebted to Miss Madge Meyers, chief dietician, for making available the necessary facilities at the Peter Bent Brigham Hospital.

†The food values for fat and calories were derived from the data of Bowes and Church.[16]

‡We are indebted to Drs. James Metcalfe and Donald M. Pitcairn, of Dr. C. Sidney Burwell's laboratory at the Boston Lying-in Hospital, for carrying out the residual air measurements.

proteins by the method of Gofman et al.[21] and that of alpha-lipoproteins by the method of Lindgren, Elliott and Gofman.[22] Serum phospholipids were determined by the technic of Bloor,[23] and total lipids by that of Bragdon.[24] The serum cholesterol, free and esterified, was measured by the method of Sperry.[25] A twenty-four-hour collection of urine was made on the fourth day of each week throughout the experiment for the measurement of creatinine by the Jaffe reaction.[26] The urine was preserved for this purpose with hydrochloric acid and thymol.

Results

Three subjects completed the regimen in all details. The fourth was unable to maintain a constant weight and retired at the end of the second week of high energy expenditure. It may be of interest to nutritionists that the subject leaving the experiment because of excessive weight gain was a tall, lean man who initially argued that no one could make him gain weight.

The food intakes in terms of daily calories and total fat are shown as individual averages and ranges in Table 1. With the exception of subject K, who was ill and vomited all or part of his meals on the forty-fourth, fifty-first and fifty-second days, the subjects were able to consume the food offered without undue difficulty. The average control levels of caloric intake ranged from 2788 to 3093 calories a day for 4 subjects. During the seven weeks of high energy exchange these intake levels averaged 5462 to 6213 calories a day. The fat intakes on the freely selected diet averaged 155 to 175 gm. The dietary fat represented 50 to 51 per cent of the total caloric supply during the control week on the free diet. During the periods of high energy exchange (Periods B and C) dietary fat represented 24.7 to 25.2 per cent of the total calories.

During the first five days of Period B it was necessary for the subjects to force these large food intakes, but when the exercise and conditioning became effective, the large meals did not appear excessive to them. The 3 subjects who completed the experimental regimen responded in different degrees so that the results are considered separately for each.

Subject H showed the largest and most regular changes of all the variables measured (Fig. 1). The density measurements for this subject indicated a significant change of body composition during Period B. The net effect could be interpreted either as a loss of obese tissue or as a gain of bone and muscle mass, and it is probable that all these changes occurred. This was associated in Period B with a probably significant lowering of the serum phospholipid ($p<0.10$)* level. Although successive measurements indicated a generally downward trend in both the alpha-lipoprotein and beta-lipoprotein levels these changes could not be shown to exceed changes readily due to chance. More important to the present problem, none of these serum lipid quantities increased during this period of doubled food intake. While weight was being gained (Period C) subject H showed a significant rise of the serum cholesterol ($p < 0.05$), the $S_f0\text{-}100$ ($p < 0.10$) and the phospholipid ($p<0.01$) levels; the alpha-lipoprotein levels were unchanged. The body-density measurements indicated an increase of body fat in Period C. During the final episode of weight reduction (Period D) the $S_f0\text{-}100$ fraction was significantly reduced ($p < 0.05$), as was the serum phospholipid level ($p < 0.10$). The body-density measurements indicated a return to nearly the original body composition.

Subject K (Fig. 2) showed minimal changes of the variables measured despite the drastic dietary

Table 1. *Averages and Ranges of the Daily Caloric Value and Fat Content of the Experimental Diets According to Periods of the Experiment.*

Age	Height	Weight	Subject		Period A (Control)		Period B (High Exchange)		Period C (Weight Gain)		Period D (Reducing)	
					calories	fat	calories	fat	calories	fat	calories	fat
yr.	*in.*	*lb.*				*gm.*		*gm.*		*gm.*		*gm.*
24	73	198	S	$\bar{x}$	3093	172	6206	174	6212	175	2273	175
				Range	2626-3474	124-202	6068-6314	164-187	6128-6298	164-180	2147-2383	171-177
24	70	155	K	$\bar{x}$	2788	155	5581	153	5558	154	2015	155
				Range	2359-3073	126-188	5178-5688	141-165	4586-5902	144-162	1852-2111	152-156
24	74	200	H	$\bar{x}$	3048	175	6213	174	5462	169	2274	175
				Range	2570-3870	118-235	6068-6314	164-187	3568-6298	147-178	2147-2383	171-177
24	76	162	O	$\bar{x}$	2813	158	5589*	154*	—	—	—	—
				Range	2248-3045	129-187	5382-5683	146-165	—	—	—	—

*2 wk. of Period B.

*Statistical tests of significance consisted of the application of "t" tests to the observed differences between periods, the last two measurements in each period being used.

and energy expenditure changes. This subject, who was relatively the least obese of all at the beginning

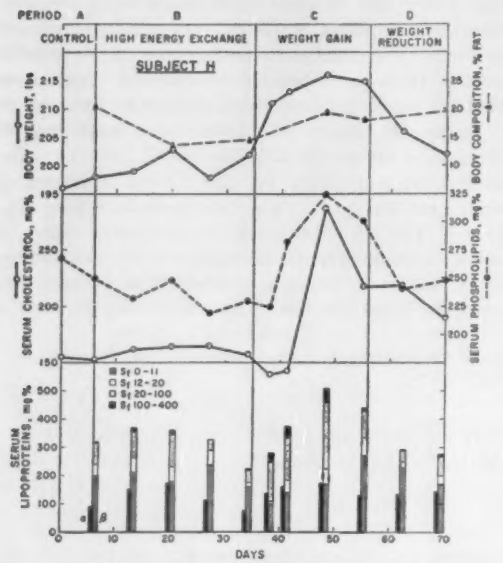

FIGURE 1. *Response of a Young Man to Alteration of Energy Exchange.*

The beta-lipoproteins are divided into four groups. The serum phospholipids represent lipid phosphorus multiplied by 25.

and who appeared to be in the best physical condi-

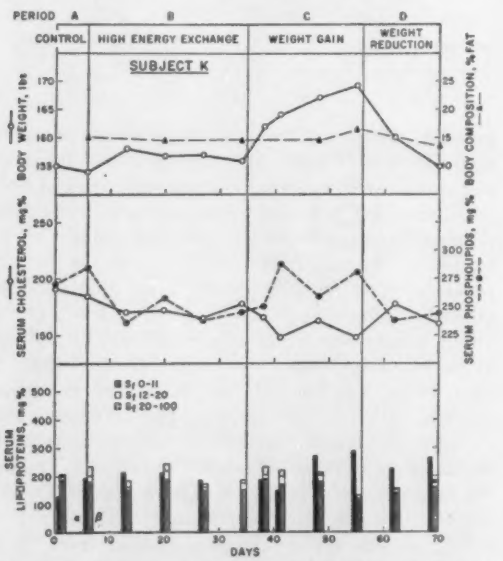

FIGURE 2. *Response of Another Healthy Male Subject to Alteration of Energy Exchange.*

The serums of this subject contained no beta-lipoprotein of the S_f100-400 group.

tion, had very little change in body composition as this was reflected in body-density measurements. The serum lipid measurements were also remarkably constant throughout the experiment, for only the serum cholesterol ($p < 0.05$) and phospholipid levels ($p < 0.10$) appeared to change, showing a decrease during the interval of high energy exchange (Period B). The body-weight increase to 168.5 pounds during Period C represented a 9 per cent increase above the control level.

Subject S (Fig. 3) displayed changes of body density and serum lipids intermediate between those of the first 2 subjects described. This subject had the highest "relative obesity" of all the subjects at the start of the experiment, and the procedures did not greatly change the net body density. Nor did the

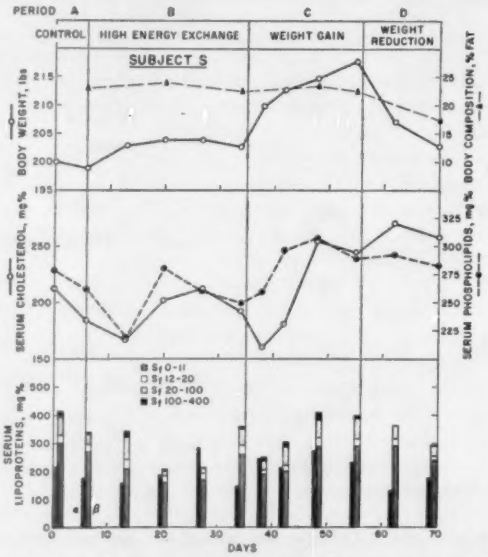

FIGURE 3. *Response of Still Another Young Man to Alteration of Energy Exchange.*

doubling of caloric intake change the serum lipid levels so long as the excess energy was dissipated with exercise. While weight was being gained (Period C) an increase of the serum cholesterol level ($p < 0.05$) occurred, and the weight loss in Period D led to a decrease of the S_f100-400 ($p < 0.10$) fraction. The changes of the serum lipids resembled those of subject H but were of lesser degree.

Subject O, who was studied for only two weeks of Period B, showed no increase of serum lipoprotein, phospholipids, cholesterol or neutral fat. The high energy exchange had produced significant increases of the body density, however.

The 4 subjects were thus unanimous in demonstrating that the large increase of food supply did not increase the serum lipids so long as the surplus energy was dissipated with exercise.

The serum total lipid levels, measured by a chemical procedure, gave no evidence that the experi-

mental regimen influenced the serum neutral fat. The measurement of total lipid was corrected with the use of arbitrary constants[28] for the contribution of phospholipids, cholesterol and cholesterol esters, and the remainder represented solvent extractable materials of which neutral fat would be the largest component. The constancy of this quantity during the large dietary changes coupled with the lack of significant changes of the low-density lipoprotein components above S_f100 indicate that lipemia — that is, serum clouding by so-called chylomicrons or large aggregates of neutral fat-protein composition — did not occur during any phase of the experiment. The proportion of esterified serum cholesterol was not changed by the experimental procedures.

The changes of the urinary creatinine measurements were not consistently related to the experimental procedures. Although these measurements were done without consideration for the creatinine content of the diet, it was expected that creatinine excretion would be influenced by the physical conditioning incurred in the high-exercise period. The product-moment correlation coefficient between the creatinine excretion expressed as milligrams per kilogram of body weight and the body-density measurement at the nearest corresponding time for the data of the 3 subjects was found to be $r=0.300$. This was not a significant correlation ($p<0.3$ that r is not equal to 0).

It was apparent that the large changes in dietary and energy expenditure influenced the subjects' water balance. During Period B the urinary volumes tended to be small and variable; in Period C large volumes occurred at variable times. During Period B it was apparent that the subjects were increasing the bulk of their musculature. Their complexions became ruddy, their tolerances to cold increased, and they were unanimous in their expressions of feeling well, relaxed and "rugged." They claimed to be able to sleep better and to work at their studies more efficiently. The high energy expenditure of Period B was facilitated by their engaging in athletic activities requiring inefficient energy expenditures and large surface heat losses. Swimming and running in bursts of speed, basketball and cycling out of doors at fast rates of speed in cold weather were found to be effective ways of expending large amounts of energy. As the men became physically conditioned they experienced increasing difficulty in maintaining constant weights and were forced to exercise both longer and more diligently.

During Period C the subjects became "fat." The faces of subjects K and H especially became round and to a casual professional observer suggested overdosage with cortisone. The subjects' shirt collars and belts became tight, their complexions became sallow, and they slept longer and fitfully. The men lost their previous *joie de vivre,* and yet they were complacent. They continued to eat the large amounts of food readily throughout Period C. During Period D with weight loss they became tired and irritable. They complained of poor efficiency at their studies and looked dimly on the experimental procedure. At least a part of the final weight loss may have represented voluntary dehydration.

Discussion

These observations indicate that young men consuming high-fat diets were able to double their caloric supply without increasing the level of their serum lipids so long as the excess energy was dissipated as exercise. The plotted data indicate a suggestion of a downward trend of the serum cholesterol and lipoprotein levels during this period of high energy turnover. These findings do not support the hypothesis proposed, which related serum lipoprotein levels to the magnitude of energy exchange. They do support the concept that serum lipid levels are related to the caloric balance of the body. The data may be interpreted in the following way. The diversion of excessive food calories to mechanical energy may lead to a favorable influence, such as facilitating low serum lipid levels as a consequence either of the increased muscle mass necessary to effect the energy loss or as a by-product of muscular work. An analogous situation may be the influence of exercise in increasing the carbohydrate tolerance of patients with diabetes mellitus. This explanation is favored by the reaction of subject K, who was originally in good physical condition and was found to have a high body density, implying a large muscle mass; he failed to show significant changes of serum lipid levels during any phase of the experiment. This resistance to change of serum lipid levels may reflect a homeostatic influence of an abundant muscle mass.

The response of 2 of 3 subjects to diversion of excess food calories to adipose tissue was an increase of serum cholesterol, phospholipid and lipoprotein levels. This occurred after a lag of seven to fourteen days. Considering the extent of the previous physical conditioning, these short lag periods seem to detract from the explanation proposed above for the failure of subject K to respond similarly. If that explanation is used it must be admitted that the failure of K to respond to fat deposition with increases of serum cholesterol and lipoprotein levels was because of a lag period exceeding three weeks, the duration of weight gain (Period C).

The increase of serum cholesterol, phospholipid and beta-lipoproteins that was associated with fat deposition in 2 of the 3 subjects confirms previous findings with 2 subjects force-fed a low-fat diet.[13] In that experiment the subjects had no preliminary physical conditioning, and 1 of them had completed a weight-losing regimen two weeks previously. That procedure may have disturbed the regulation of his

serum lipid levels. The serum lipid increases in those 2 subjects occurred at about the fifth and seventh days of the weight-gaining phase. Body-composition studies were not done in that experiment, but there were gross indications of a real increase of body fat.

The alpha-lipoprotein levels were not significantly changed in the present experiment. The beta-lipoprotein levels were changed, as has been indicated, but they appeared less sensitive to these influences than the serum cholesterol levels. The deposition of adipose tissue led to an increase of the levels of both the serum beta-lipoproteins of the S_f0-100 classes and the cholesterol. These levels were thus not dissociated by the procedures. The product-moment correlation coefficient between the serum total cholesterol and the S_f0-11 for the combined data of the 3 subjects who completed the experiment was 0.581, which, with 33 degrees of freedom, was highly significant ($p < 0.01$). This correlation is of the magnitude usually found in human material.[2] This experiment has not reproduced the unique dissociation of serum cholesterol and lipoprotein seen in the Central American vegetarian subjects referred to above.

The changes in body weight observed during the present experiment were surely indicative of real changes of body composition. However, the body-density measurements are difficult, if not impossible, to interpret despite the advantage obtained by the relative nature of the measurements of each subject in relation to his original measurement. Aside from the technical difficulties of obtaining accurate submerged weights, which require precise co-operation and some self-assurance of the subject when he is underwater, the density measurement obtained represents the net buoyancy of a body composed of several materials, each differing in density and capable of independent variation. In the present experiment one effect of exercise and conditioning must have been to increase the muscle mass, and another to increase the skeletal mass and probably its density. At the same time the body adipose tissue may have decreased. All these simultaneous changes, coupled with minor changes of hydration, tend to obscure the use of these body-density measurements in the appraisal of fat content of the body. The absence of more dramatic decreases of body density during the weight-gaining phase (Period C), when the men showed physical signs of increasing adiposity, may have resulted from a continuing accretion of high-density bone and muscle mass under the stimulus of the physical training of Period B.

The creatinine excretion, which in theory is a measure of body-muscle mass, has not proved a sensitive indicator, and the present data conform with previous reports of the limitations of this index.[26,27]

The experiment described may represent in a microcosm the nutritional progress of an adult American male. A period in early adulthood of high energy turnover associated with athletic endeavors is followed by a long period of diminishing physical activity but with unchanging dietary habits. This leads in a variable time to an obese person at middle age, with poor muscular development and with elevated serum cholesterol and beta-lipoprotein levels although without visible lipemia. More important, there is generally significant atherosclerosis in such a man. The present experiment may have shortened these simulated phases excessively. By not allowing time for the large changes of body inventory, it may have minimized or obscured the full effects on the serum lipids. There seems little doubt that significant effects can be produced on both the body composition and the serum lipids in most subjects by these alterations of diet and physical activity.

It would be of interest to know whether a larger sample of this age or a sample of older subjects would have shown a similar degree of response. The 2 subjects studied previously,[13] each of whom responded promptly to positive caloric balance with increases of the serum lipoproteins and cholesterol, were twenty-seven and thirty-eight years of age. The present subjects were in the age group (twenty-four years) in which there is both anatomic[28] and chemical evidence[29] that atherogenesis is beginning.

The serums drawn in the postabsorptive state were clear throughout the experiment. The lack of increase either of neutral fat as measured chemically or of low-density beta-lipoproteins measured with the ultracentrifuge conforms with the observation that the serum lipid changes that occur with positive caloric balance and adiposity are of the invisible, high-density beta-lipoproteins. It should be emphasized that visible lipemia in serum obtained in the postabsorptive state is uncommon in subjects of any age and cannot be a *sine qua non* for the development of atherosclerosis.

The subjective responses of these men to the experiment reveal two observations of possible clinical usefulness. Although the first days of physical training produced discomforts and fatigue, the men soon experienced a sense of well-being and accomplishment that they considered adequate compensation for their troubles. During the period of low exercise and weight gain that followed, they continued to take the excessive amounts of food without complaint and even with some relish, but as they grew fat they became sluggish and, in their own evaluation, less efficient in their daily activities. Nevertheless, they were complacent in this progress of obesity. The first reaction may mean that physical conditioning is self-rewarding and sufficient motivation in itself aside from any desirable effects that it may have in preventing atherogenesis. The second

reaction indicates that dietary habits, even when of short duration, are associated with great inertia. This tardiness of adjustment of food intake to metabolic requirements may be based on obscure physiologic phenomena that are in addition to the contribution made in real life by social customs, culinary artistry and changing values of pleasurable activities that occur with age.

Summary

Experiments with human subjects demonstrated that doubling the caloric supply of young men did not increase the serum lipoproteins and cholesterol levels so long as the surplus energy was expended as heat and muscular energy. Accretion of this excess energy as adipose tissue caused the serum lipid levels to increase in 2 of 3 subjects.

These experimental findings are related to the development of obesity, increased serum lipid levels and atherosclerosis by American men. It is proposed that positive caloric balance over a long period elevates the serum lipid levels and contributes to atherogenesis.

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PANCREATITIS*

Observations on 131 Patients

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MANY articles on pancreatitis have dealt with the etiology,[1-5] pathology,[6-8] diagnosis[9-13] and various forms of treatment.[14-20] The purpose of this paper is to put more emphasis on the question of prognosis than has been done previously, as well as to comment on some unusual manifestations of the disease.

Material

Between January 1, 1946 and December 31, 1952, 131 patients were treated for pancreatitis in the West Roxbury, Framingham and Boston Veterans Administration hospitals. For clinical convenience the cases have been classified as proved (108 patients) or presumptive (23 patients). To be placed in the former group a patient must have had clinical manifestations consistent with pancreatitis, with an elevation of the serum amylase, or else pancreatitis must have been found at operation or post-mortem examination. The presumptive group included cases in which the history and physical findings, gastrointestinal series and cholecystograms indicated pancreatitis as the most likely diagnosis but in which the serum amylase was not elevated and operation or autopsy not done. The 108 cases in the proved group were further divided into acute and chronic. Fifty-five patients were seen in their initial or acute attack. Although 20 of them had later attacks else-

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where and became chronic cases, these attacks were not observed by us. The initial attacks had been, in our opinion, the focal point of the illness and seemed to justify placing these cases in a separate group. The remaining 53 of the 108 patients with proved pancreatitis were those who had multiple attacks under our observation and in whom the chronic form of the disease was most susceptible of analysis. The cases termed presumptive have been omitted from the statistical analysis, which has been drawn from the proved cases only. There were 130 males and 1 female, a sex ratio in keeping with the distribution of patients at these hospitals.

Pathology

The variegated pathological picture of pancreatitis has been well described by Fitz,[6] by Elman[7] and by Baggenstoss.[8] Fat necrosis, edema, hemorrhage, necrosis and suppuration of the pancreas were found alone or in combination in the 46 cases in which specimens were available. Thirty-nine were confirmed at operation, and the remaining 7 at autopsy.

Etiology

The etiology of pancreatitis is unknown. The presence of alcoholism and concomitant gall-bladder disease are among the most commonly suspected etiologic factors.

Alcoholism

Of the 108 patients with proved pancreatitis 55, or 51 per cent, drank to excess. In this group the initial attack or exacerbation appeared to be precipitated by an alcoholic bout. That alcohol is by no means a universal etiologic factor is shown by the fact that 27, or 25 per cent, were abstainers.

Gall-Bladder Disease

Of the 108 proved cases 35, or 32 per cent, had gall-bladder disease in some form. Of them, however, only 14 (13 per cent of the total) had gallstones. In 2 patients there was typical acute cholecystitis without stones. Fourteen had microscopical evidence of cholecystitis but no stones; these cases were found at incidental cholecystectomy at the time of elective choledochostomy for pancreatitis. The remaining 5 patients of the 35 with gall-bladder disease had cholecystectomies at other hospitals, with a microscopical report of acute cholecystitis without stones. In the 14 patients without gallstones but with microscopical evidence of cholecystitis the biliary disease was probably secondary to pancreatitis. The 13 per cent occurrence of gallstones in the group is lower than that usually reported,[2] probably because this series consists almost entirely of male patients. The percentage, however, is still higher than one would expect as an incidental finding in a male population of this age and is surely of some significance etiologically. In several patients abnormal cholecystograms were found in the stage immediately after recovery from the attack of acute pancreatitis.[21] Cholecystograms repeated at a later date were normal. It is obvious that in this group of patients a diagnosis of cholecystitis might frequently have been made if further study had not been carried out.

Diagnosis

Clinical Manifestations

An analysis was made of the symptomatology and physical findings in the 55 acute cases. Since the detailed results differ in no way from clinical pictures described by others[9,13] they are omitted from the report. Jaundice occurred in 7 of the 55 acute cases and was due to common-duct stone in only 1 patient and to pancreatic edema in the others. Gastrointestinal bleeding manifested by melena was seen in 4 of the acute cases. This led to a mistaken diagnosis of infarcted bowel in 1 patient. The bleeding seemed to be due to inflammation of gastroduodenal mucous membrane — by contiguity from the acutely inflamed pancreas.

Laboratory Data

Serum Amylase

The upper limit of normal for serum amylase in the laboratories of these hospitals is 200 mg. per 100 cc. by the Somogyi method. In 36 of the 55 acute cases, or 65 per cent, the diagnosis was proved by elevation of the serum amylase combined with a consistent history and physical findings. In the other 19 it was proved at operation or at autopsy. In general the more severe clinical pictures were associated with the higher amylase determinations. We found, however, that acute hemorrhagic pancreatitis that went on to fatal termination was accompanied by a normal serum amylase in 2 patients. This has been postulated as due to the extreme destruction of the gland. In this series the amylase determinations, although not performed daily, were frequent enough to demonstrate that the amylase returns to normal an average of five days after onset of the symptoms, the range being two to nineteen days.

In the 53 patients with chronic pancreatitis an elevated serum amylase was not observed in 27, or 51 per cent, at any time despite repeated determinations during various hospital admissions. Of the remaining 26 (49 per cent) of the patients whose amylase levels were elevated, determinations were done in only 11 patients frequently enough to indicate a trend. In these cases, again, on the average, the amylase returned to normal five days after the onset. Since only 65 per cent of the acute and 49 per cent of the chronic cases demonstrated an elevated serum amylase during the course of the disease it is assumed that many cases go unrecognized. It is

necessary to draw blood early (within the first twenty-four hours of an attack) and daily to increase the number of correct laboratory diagnoses.

Blood Sugar

In 14 of the 55 acute cases the fasting blood sugar on admission was over 130 mg. per 100 cc., ranging to a level of 416 mg. per 100 cc. This was a transitory rise except in 1 patient, who was known to be diabetic. Even though a patient with pancreatitis may have a long and significant history of alcoholism diabetic coma should be considered as an alternate diagnosis to the more common hepatic coma on the basis of decompensated cirrhosis. Of the 53 patients with chronic pancreatitis diabetes mellitus was present in 12. In this group calcification of the pancreas was seen on x-ray examination in 9 patients.

X-Ray Findings

X-ray studies in pancreatitis can show pancreatic calcification, hydrothorax and deformities of the gastroduodenal segment on barium study, as well as evidence of biliary disease or dysfunction, as already mentioned. The finding of a dilated loop of small intestine in an acute attack is frequent and may simulate small-bowel obstruction.

Hydrothorax occurred in 5 patients. It was located on the left in 3 and on the right in 2. In 1 case this led to thoracotomy rather than to treatment of the primary disease, pancreatitis.

Significant extrinsic pressure on the upper gastrointestinal tract was noted in 7 cases. In 1 unusual case of chronic pancreatitis the gastrointestinal series was reported as showing a picture of hourglass stomach that was thought to be due to ulcer. Operation disclosed pancreatitis, which had caused marked retraction of the pylorus to the left, giving the picture described above; the hourglass was actually the pyloric ring.

In 20, or 35 per cent, of the chronic cases x-ray examination showed calcification of the pancreas.

Treatment in Acute Cases

The treatment of acute pancreatitis was nonsurgical and was carried out with several aims. The first of these was suppression of pancreatic function by constant gastric suction and the administration of atropine. The second was control of pain by the use of Demerol hypodermically and, less frequently, procaine blocks of the celiac axis and splanchnic nerves or appropriate epidural area. Splanchnic blocks were done in 8 patients, in 3 of whom there was complete relief of pain for several hours. In 4 others the effect was more transitory, lasting less than an hour, and in 1 the block was ineffective. Two thoracic epidural blocks gave complete relief, which was maintained for several days. Celiac blocks were done in 1 patient, with relief of pain for several hours. The third purpose of therapy was to counteract the "infectious component" of the disease; this was obtained by intramuscular injection of penicillin and streptomycin. Appropriate fluid and electrolyte replacement including blood, plasma and albumin, was also necessary, as was insulin therapy, when indicated for acute diabetes. Finally, calcium gluconate, approximately 1 gm. a day intravenously, was given to correct calcium deficiencies if present.

Results of Nonsurgical Therapy

Fourteen, or 56 per cent, of the 25 patients followed who were treated nonsurgically had further attacks, and only 9, or 36 per cent, remained asymptomatic. Two died of their disease, 1 on the first and the other on the eighth day. The period of observation averaged thirty-one months, with 3 patients lost to follow-up study. Although the mortality in this group was only 8 per cent over half the patients so treated continued to have attacks of pancreatitis, emphasizing the fact that conservative therapy in itself, although it results in a low mortality for the individual attacks, does not prevent further attacks in the majority of patients so treated.

Results of Initial Nonsurgical Therapy Followed by Surgery

Despite our desire to treat acute pancreatitis nonsurgically, definite indications existed for operation because of various complications and associated conditions.

Gall-bladder disease. In 12 patients, after the acute episode had subsided, cholecystectomy, with or without common-duct drainage, was carried out for gall-bladder disease. Of the 8 patients who had common-duct drainage for twenty days to four months 7 are asymptomatic, and 1 is unimproved; the remaining 4 patients did not have common-duct drainage. One of them died (mortality of 8 per cent) of pancreatic abscesses causing common-duct obstruction three months after operation, 1 is unimproved, and the remaining 2 are asymptomatic. The follow-up period in this group averaged thirty-two months. The best results were obtained in these patients with associated gall-bladder disease, 9 (75 per cent) of them being asymptomatic and only 2 (17 per cent) having had further attacks. It appears that the least imperfect therapeutic program developed in our study was the nonsurgical therapy of the pancreatitis followed by the surgical treatment of any coexisting biliary-tract disease when the patient had recovered.

Pancreatic abscess. Two of the 4 patients operated on for drainage of pancreatic abscesses died, 1 in two weeks of a pulmonary infarct and the other in three weeks of common-duct obstruction secondary to inflammation in the head of the pancreas. Of the remaining 2, 1 is well, and the other continued to have attacks of pain after forty-two months of follow-up study.

Pancreatic cyst. One patient, after weeks of nonsurgical therapy, had a pseudocyst of the pancreas

anastomosed to the duodenum, and he has been asymptomatic during a follow-up period of a year.

Mistaken diagnosis. Of the 10 patients operated on with a mistaken diagnosis, 4 died — 1 on the day of the operation and the remainder on the second, eighth and twelfth days postoperatively. Over a short-term follow-up period of a year, 3 have had no further attacks, and the remaining 3 have had recurrent attacks requiring further hospitalization with or without surgery during a follow-up period of two or three years. In 8 of them the procedure was limited to laparotomy. One had a cholecystectomy; the other, who had a cholecystostomy, was a forty-one-year-old man (W.R. VAH—R 33882) admitted with a one-week history of left-upper-quadrant pain, tenderness, nausea and vomiting. A diagnosis of acute duodenal ulcer had been made by his doctor. On admission he was restless, jaundiced and confused. The serum amylase was 100 mg. per 100 cc. Because of the development of a mass in the left upper quadrant and the passage of bright-red blood by rectum a diagnosis of infarcted bowel was made. At operation the patient was discovered to have acute hemorrhagic pancreatitis. Cholecystostomy was done, and the lesser omental cavity drained. He died two hours later. The blood sugar was 416 mg. per 100 cc. Postmortem examination showed acute hemorrhagic pancreatitis.

This history brings out three points that must be borne in mind when one deals with pancreatitis: the serum amylase was normal during an attack of hemorrhagic pancreatitis; the patient had acute diabetes mellitus; and there was passage of bright-red blood by rectum.

Results in All Acute Cases

Results of treatment show that in the entire group of acute cases, regardless of therapy, 23 (44 per cent of the 52 followed) are asymptomatic and 20 (39 per cent) continue to have further attacks of pancreatitis. The mortality was 17 per cent. As noted above, emergency surgery with a mistaken diagnosis carried a high mortality, and the best results were obtained in patients with associated gall-bladder disease who had cholecystectomy with or without choledochostomy after the acute attack of pancreatitis had subsided.

Treatment in Chronic Cases

The diagnosis was simpler in the 53 patients with chronic pancreatitis than in the acute cases, but one must be wary of unrelated surgical emergencies masquerading as acute exacerbations in patients with chronic relapsing pancreatitis. More than one form of therapy was used in some of these cases during the various admissions.

Results of Nonsurgical Treatment

Nine of the 16 patients followed are unimproved. Four are well, and 3 died — 1 after development of retroperitoneal abscesses secondary to pancreatitis, 1 from cirrhosis of the liver, with calcification of the pancreas, and the third from carcinoma of the esophagus. The follow-up period ranged from seven months to six years, with an average of three and a half years. Two patients could not be traced. It is interesting that although conservative therapy has not been considered satisfactory in the prevention of recurrent attacks, 4 of these patients have been asymptomatic over a three-year period, suggesting the possibility that the disease has "burned itself out" in these patients.

Results of Surgical Treatment

Prolonged common-duct drainage. Fourteen patients were subjected to prolonged common-duct drainage with good long-term results in 3 (27 per cent) of the 11 followed. It should be emphasized that no attacks of pancreatitis occurred with the T tube in place and draining, but attacks occurred when T tubes were clamped off or removed so that 8 patients (73 per cent) were unimproved, including 1 who died of his disease on the fifth postoperative day. The T tubes were left in place for five days to eight months, with an average of three months. Follow-up periods ranged up to three years, with an average of two and a third years in the 11 patients. The universal protection against recurrent attacks with the common-duct tube open seems a significant phenomenon that has obvious implications concerning the proper type of operation to strive for — namely, one that accomplishes continuous free internal biliary drainage.

Drainage of pancreatic cyst. Three of the 7 patients operated on for pancreatic cyst continue to have attacks, and 4 are well. Treatment in the 3 who are unimproved consisted of resection in 1, cystduodenostomy and subtotal gastric resection in the second and a cystgastrostomy in the third. Of the 4 who are well 3 had external drainage, and the other a cystgastrostomy. Follow-up periods ranged from one to five years, with an average of two years.

Sphincterotomy. Of the 6 patients who had sphincterotomy, only 1 is well two years later. Two died — 1 two months after operation, no cause being found for his death, and the other three months postoperatively with a massive retroperitoneal hemorrhage. The remaining 3 patients (50 per cent) are unimproved; 1 received surgical treatment in another hospital two months later, without improvement in his symptoms, the second had bilateral splanchnicectomy after seven months, without improvement, and the third had a subtotal gastric resection five months later. Our conclusions are of necessity tentative because of the limited number of patients. We cannot explain the discrepancy between our results and those of Doubilet and Mulholland.[15]

Splanchnicectomy. Two of the 5 patients who had splanchnicectomy are asymptomatic, and 3 continued to have the same symptoms after operation. Follow-

up periods ranged from two to seven years, with an average of four years. The procedures were bilateral, including not only the splanchnic nerves but also the sympathetic ganglions from the eleventh to the twelfth dorsal segment.[20]

Partial gastrectomy. Partial gastrectomy was done on 3 patients. One died three months postoperatively, the cause of his death being unknown. The second was unimproved two years later, and then had a vagotomy and in seven months a sphincterotomy; he is still unimproved. There was no follow-up study of the third patient.

Exploratory laparotomy. Three patients had exploratory laparotomy for another and mistaken diagnosis. Follow-up study in 1 of these two years later showed no improvement.

Partial pancreatic resection. Resection of the tail of the pancreas for localized disease was carried out in 2 patients, both of whom were unimproved five years later. In 1 the symptoms were relieved immediately after operation, but as the disease apparently progressed symptoms recurred. Anastomosis of the distal pancreatic duct to the small bowel may have a place in the treatment of this type of patient.

Simple cholecystectomy. This operation was done in 1 patient. Examination four years later showed that he had not improved.

X-ray therapy after surgery. One patient was given 300 r, and after a three-year follow-up period he is asymptomatic. This form of therapy was suggested because of the known fact that surgical parotitis responds to radiation therapy. Despite this 1 successful case, we have been disappointed with the results of x-ray therapy in groups observed at other hospitals and have not pursued it further.

Results in All Chronic Cases

The number of procedures carried out in the 53 patients was 60 — 4 patients having multiple procedures. No one procedure produced statistically significant good results. We are forced to agree that the variety of procedures employed in the treatment of this disease is a reflection of the inadequacy of the individual methods.

Prognosis

Nine of the 108 patients with proved pancreatitis did not survive the initial attack, an 8 per cent initial mortality. Follow-up study of 88 of the 99 survivors revealed that 7 more had died — 4 (5 per cent) of the disease, 1 of cancer of the esophagus and 2 of unknown causes. The total mortality was therefore 13 per cent.

Twenty-three (26 per cent) of the 88 patients followed had only one attack whereas 65 (74 per cent) had further attacks. Further breakdown of the latter group revealed that, of the 58 remaining, 15 (26 per cent) were asymptomatic at the time of this study and 43 (74 per cent) were still having attacks (Table 1).

Discussion

Since this series, with 1 exception, was composed wholly of males, there was a lower prevalence of gall-bladder disease (32 per cent) and a higher prevalence of alcoholics (51 per cent) than in most other series.

Serum amylase determinations were not as consistently helpful as elsewhere reported, being elevated in only 65 per cent of the acute and 45 per cent of the chronic cases. This test should be done in the first twenty-four hours and repeated daily during an attack. In addition, blood studies for lipase determinations and urinary diastase levels should increase the percentage of correct diagnoses before surgery or autopsy.

Table 1. *Prognosis in 108 Cases of Pancreatitis.*

Progress of Disease		No. of Patients		Percentage
Recovery from initial attack		99		
Death from initial attack		9		8
Only 1 attack		23		26
Multiple attacks		65		74
No further symptoms	15		26	
Continued attacks	43		74	
Subsequent death	7		5	
Of pancreatitis	4			
Of carcinoma of esophagus	1			
Of unknown cause	2			

Transitory elevations of blood sugar, as well as diabetes mellitus, gastrointestinal bleeding and hydrothorax, were observed. The first two conditions could result in the loss of the patient's life if they were not looked for and adequately treated. The last two can result in a mistaken diagnosis, with disastrous consequences.

On the basis of this experience nonsurgical treatment is considered the procedure of choice in an acute attack or in an exacerbation in a chronic case. The recurrence rate is over 50 per cent in the patients so treated, but the mortality is lower than that in those operated on as emergencies. The most encouraging results were obtained in patients with associated gall-bladder disease who had the indicated therapy after nonsurgical treatment of the acute attack of pancreatitis. The best therapeutic attack, then, appears to be that of the limited objective—the acute attack of pancreatitis is treated, and any associated biliary disease corrected later. Which type of therapy to use in the patient with chronic relapsing pancreatitis without gallstones cannot be decided from these data. The absence of attacks while the common-duct tube is in place and draining makes one lean toward a type of operation that will direct the flow of bile from the duodenum.

We found that the initial mortality was 8 per cent and the late mortality 5 per cent, and that there was a 26 per cent chance that the patient would have only one attack and a 74 per cent chance that he would have multiple attacks.

Summary

During the period January 1, 1946, to December 31, 1952, 131 patients with pancreatitis were treated in West Roxbury, Framingham and Boston Veterans Administration hospitals. The 108 proved cases were studied.

A higher prevalence of alcoholism and a lower prevalence of biliary disease was observed than in most other series.

Amylase studies were not as helpful as elsewhere reported.

The frequency of transitory blood sugar elevations, diabetes mellitus, hydrothorax and gastrointestinal bleeding is reported.

Experience with therapy is described. The policy of therapy, based on limited objectives is outlined.

The protracted nature of the disease is discussed.

We are indebted to Drs. Richard Warren and Henry H. Faxon, under whose direction this project was conducted.

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HYPONATREMIA IN THE UROLOGIC PATIENT

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DURING the past ten years the danger of giving patients (particularly those with impaired cardiac function) too much sodium has frequently been stressed. However, the opposite danger of hyponatremia, or a low sodium level, has received very little emphasis and for this reason has often not been recognized. Time does not allow a general discussion of electrolyte balance, which has been more than adequately covered by numerous books and papers on the subject. Actually, this great volume of work has made the subject seem unduly complex. In this purely clinical paper I wish to emphasize the facts that low sodium levels are not uncommon in the urologic patient and that the recognition of this syndrome is of the utmost importance. During the last two years I have seen 6 cases of proved hyponatremia, which are briefly reported. I also wish to emphasize the point that it is possible to make a presumptive diagnosis of sodium deficiency without extensive laboratory facilities. There are several reasons why sodium deficiency is particularly likely to develop in the urologic patient.

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In the first place many urologic patients have cardiac complications and therefore may have been on a low-salt diet before entering the hospital, so that when they are first seen by the urologist they are already in a state of salt depletion. This is particularly likely if, in addition to a low-salt diet, they have been receiving a mercurial diuretic.

Secondly, the routine treatment of the urologic patient is designed to promote a diuresis by forcing fluids and relieving back pressure on the kidneys due to mechanical obstruction. However, many of these patients have pre-existing renal disease, with tubular damage, and may not be able to conserve sodium efficiently. If, in this type of patient, a diuresis is established excessive amounts of sodium will be lost.

This salt loss will be greatly increased if, as the internist often insists, they are given intravenous infusions of fluid containing no salt.

Thirdly, the salt intake of many urologic patients is low because for various reasons they often take very little solid food by mouth.

Finally, in rare cases there may occasionally also be an element of adrenal failure, with resulting loss of salt that would normally be retained in times of stress. As soon as there is a decrease in the sodium concentration of the extracellular fluid there will at once be a compensatory loss of water. This reduces the total volume of the extracellular fluid and plasma, with a resulting decrease in renal blood flow and consequent renal failure. The signs of dehydration will develop, and since this dehydration is due primarily to salt loss it is obvious that the larger the amount of hypotonic fluid given, the worse the dehydration will become. It is also obvious that because of this compensatory mechanism the patient may actually be in a state of salt depletion even with low-normal blood sodium levels. The sodium level will not drop below normal until the salt and water loss has become severe. Associated with the loss of sodium there is a loss of chloride. However, from the purely practical point of view, it is usually not necessary to be concerned with the chloride loss or with disturbances in the other electrolyte levels. It would be ideal if a complete study of the fluid and electrolyte balance of every urologic patient could be made, but such studies are unfortunately expensive, tedious and often beyond the available facilities. For this reason it is important to be on the watch for possible sodium depletion and to be able to make the diagnosis clinically, which I believe can usually be done.

The first thing that should alert the urologist to the possibility of salt depletion is a history of a low salt intake. Azotemia without evidence of severe renal damage or a large urinary output associated with a rising nonprotein nitrogen should at once suggest the possibility of hyponatremia. A rising nonprotein nitrogen in spite of an adequate urinary output was present at first in all but one of the 6 cases reported below. Another finding that has usually been present and is likewise due to a decrease in the extracellular fluid has been the clinical appearance of dehydration in spite of adequate or more than adequate fluid intake. If the patient's tongue is dry and coated in spite of an intake of 3000 cc. of fluid the possibility of hyponatremia should at once be considered. Weakness and general debility are present, and are always greatly in excess of what seems warranted. The most striking symptom, however, is the loss of appetite and inability to take anything by mouth. Although the diagnosis can, of course, be proved only by the finding of a low sodium level in the blood I believe that the clinical findings as outlined above are sufficiently definite to warrant the giving of salt even in the absence of laboratory confirmation. If the hyponatremia is not too severe the intravenous administration of 1000 cc. of physiologic saline solution will result in a striking and rapid improvement, which confirms the diagnosis.

The treatment of severe sodium depletion is the intravenous administration of hypertonic saline solution and sodium lactate. However, my experience has been that an adequate clinical response can usually be obtained by intravenous administration of physiologic saline solution accompanied by moderate amounts of sodium chloride by mouth. On this regimen it will be several days before the sodium levels return to normal, but since the total sodium loss cannot be accurately measured it seems to me dangerous to try to correct the electrolyte balance rapidly by the administration of large amounts of sodium at one time. It is surprising how rapidly the nonprotein nitrogen drops and the patient's general condition improves with only small amounts of sodium chloride. As soon as the extracellular fluid volume returns to normal a marked diuresis occurs, even if the sodium level is still slightly below normal.

Of the 6 cases reported below, hyponatremia developed in 5 after relief of long-standing back pressure due to prostatic obstruction. In 3 cases it appeared preoperatively while the patients were on urethral drainage. In the other 3 the sodium deficiency was first recognized postoperatively; however, in retrospect, it appears obvious that in these cases a mild degree of salt depletion must have been present, although unrecognized, at the time of operation. Three of the 6 patients had been on a low-salt diet before entering the hospital, and 2 had evidence of severe renal damage. In the interest of brevity only the most significant facts concerning these 6 cases are presented.

Case Reports

Case 1 (S.H. 93320). A 65-year-old man with carcinoma of the prostate and long-standing chronic retention had been on a low-salt diet, and on entry to the hospital his bladder was emptied by means of an inlying urethral catheter. Because of arteriosclerotic heart disease with atrial fibrillation an internist continued the low-salt diet and mercurial diuretics. The patient's general condition seemed fair, and he took food and fluids by mouth freely. He had both a large fluid intake and a large fluid output but did not improve in spite of adequate urinary drainage. On the 6th hospital day the nonprotein nitrogen was found to be twice the value it had been on entry, and accordingly complete electrolyte studies were made (Fig. 1). As a result of these studies, which showed a sodium level of 131 milliequiv. per liter, the low-salt diet was stopped, and the patient was given sodium chloride intravenously and by mouth. This was followed by a marked diuresis, a rapid drop in the nonprotein nitrogen and striking improvement in his general condition. A transurethral prostatic resection and a bilateral orchidectomy were done. He made an uneventful convalescence and when last seen was getting along well on a normal diet.

This case is typical of the low-salt syndrome. The patient entered the hospital in a state of salt depletion, which was increased by the low-salt diet and the use of mercurial diuretics. Relief of the back pressure on the kidneys resulted in a diuresis. Because of previous kidney damage he was unable to retain salt so that still further salt depletion occurred. This excessive loss of salt and water resulted in a decreased renal blood flow, further kidney damage and rapidly rising nonprotein nitrogen. It was surprising how quickly and easily this condition could be corrected. At no time was the patient given more than 15 gm. of salt a day in addition to the salt in his food. On the other hand, if this condition

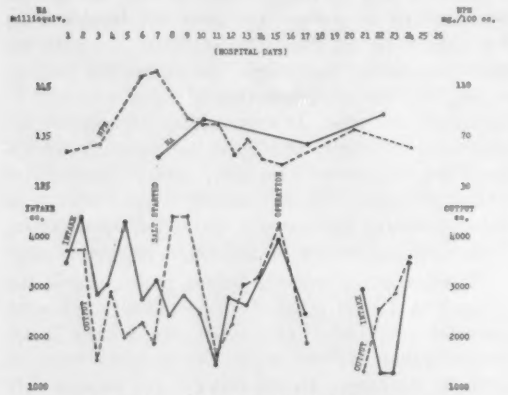

FIGURE 1. *Electrolyte Studies in Case 1.*

had not been recognized in time, I am sure it would have been fatal as it was in the following case, which was identical with Case 1 except that the patient was not on a low-salt diet.

CASE 2 (S.H. A2049). A 74-year-old man entered the hospital with a greatly distended bladder and a history of long-standing chronic retention. On admission the nonprotein nitrogen was 85 per 100 cc. He was treated by forced fluids and drainage with a urethral catheter. During the 1st week in the hospital he had a diuresis, and the nonprotein nitrogen dropped to 58 mg. per 100 cc., but during the 2d week his condition deteriorated and the nonprotein nitrogen rose rapidly to 105 mg. per 100 cc. Unfortunately, electrolyte studies were not done until he had been in the hospital 2 weeks, at which time the sodium level was found to be only 114 milliequiv. per liter. In spite of the administration of hypertonic sodium chloride this low level was never adequately corrected, and he died 10 days later of uremia, acidosis and hyponatremia.

The following case represents a much less serious situation but is more significant because it demonstrates that sodium depletion may develop in a patient who is not particularly sick and that the diagnosis can be made clinically without laboratory help.

CASE 3 (S.H. A11213). An 85-year-old man with heart disease entered the hospital with benign prostatic hypertrophy and carcinoma of the bladder. He had 200 cc. of residual urine and a normal intravenous pyelogram. Before admission he had been on a low-salt diet and had been receiving a mercurial diuretic. It was known, however, that he had not followed his diet strictly. After entry to the hospital the low-salt diet was continued, and he received 1 injection of mercury. A transurethral resection of the carcinoma of the bladder and of the prostate was done without difficulty. For 3 days after operation he received 5000 cc. of 5 per cent glucose in water intravenously (Fig. 2). He seemed very well on the 1st postoperative day, but less well on each succeeding day. He became weak and listless, and lost his appetite. His tongue became dry, and the clinical appearance of dehydration developed in spite of an adequate fluid intake. On the 3d day I was certain that this patient had a salt deficiency, but I had great difficulty in convincing the internist who was in charge of the cardiac condition that this was a fact. Unfortunately, since it was Sunday, it was impossible to have electrolyte studies made until the following day. A compromise was reached, and the patient was taken off the low-salt diet and given 500 cc. of physiologic saline solution intravenously. This infusion was given on Sunday morning, and by Sunday afternoon there had been a tremendous improvement in his condition.

The sodium level on the following morning was 134 milliequiv. per liter. He was given a moderate amount of salt by mouth and continued to improve, although the sodium level in the blood never reached the minimum normal level of 136 milliequiv. per liter. After the administration of salt there was a marked diuresis, and the nonprotein nitrogen, which had risen rapidly from 43 mg. to 72 mg. per 100 cc. because of salt depletion, returned to normal.

This case shows that although it is certainly necessary to restrict the salt intake in cardiac patients, one must be constantly on the alert to be sure that,

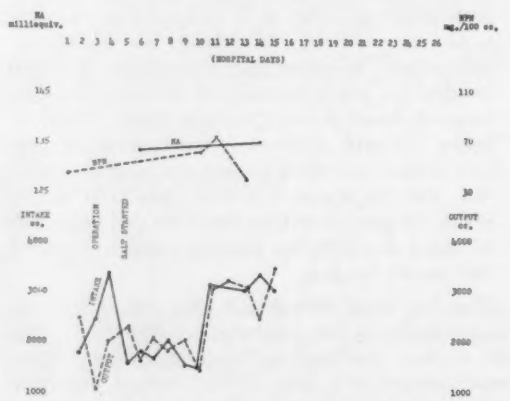

FIGURE 2. *Electrolyte Studies in Case 3.*

as a result of this restriction, hyponatremia does not develop. It also shows that severe azotemia may develop from salt depletion even in the absence of intrinsic renal disease.

CASE 4 (S.H. A6153). A 74-year-old man entered the hospital with a large amount of residual urine that had obviously been present for a long time. (This case is so similar to Case 3 that it does not warrant reporting in detail; the only difference is that the patient was not on a low-salt diet postoperatively.) Because of persistent hiccups he took very little food by mouth, and because of arteriosclerotic heart disease he was given an intravenous infusion of fluid containing no sodium. He failed to improve as had been expected, and marked weakness, listlessness and loss of appetite developed. On the 9th postoperative day the blood sodium was 134 milliequiv. per liter, and the nonprotein nitrogen had risen to 50 mg. per 100 cc. After he had been given salt by mouth and 1000 cc. of physi-

ologic saline solution intravenously on 3 successive days there was a great improvement in his general condition, and the nonprotein nitrogen dropped to 30 mg. per 100 cc.

In the following case severe acute postoperative adrenal failure was probably associated with salt depletion:

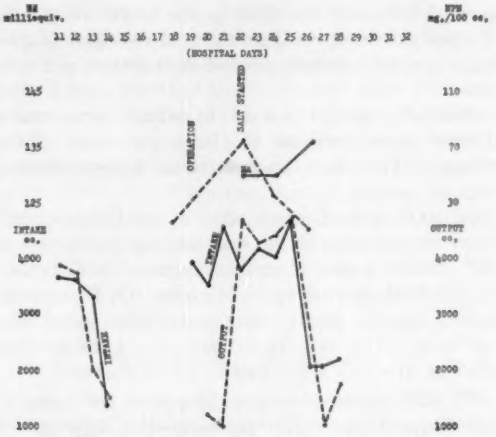

FIGURE 3. *Electrolyte Studies in Case 5.*

CASE 5 (L.H. 13984). A 65-year-old woman had previously had a pyelolithotomy on the right. She entered the hospital for the 2d time in April, 1954, with an obstructive stone in the left ureter and several stones in the left kidney. A ureterolithotomy on the left was done on April 15. Convalescence was complicated by persistent vomiting, and she was given a considerable amount of glucose and water intravenously. On May 1 her condition seemed good, and a pyelolithotomy on the left was done without incident. Postoperatively, her general condition was fair, and she was given fluids by mouth and large amounts of glucose and water intravenously. On the 3d postoperative day severe medical shock, which could easily have been mistaken for coronary thrombosis or a cerebral accident, suddenly developed. The electrolyte studies, however (Fig. 3), showed low sodium and potassium levels. The patient made a rapid and dramatic recovery with sodium, potassium and plasma intravenously accompanied by large doses of cortisone.

In retrospect it is obvious that at the time of operation, although the patient seemed perfectly well, she was in a state of electrolyte imbalance. It seems probable that, because of previous emotional and surgical stress, the adrenal glands had become exhausted and postoperatively were unable to conserve sodium properly. This case demonstrated very dramatically the danger, first, of giving too much glucose and water intravenously without an adequate salt intake and, secondly, of operating on a patient who has recently been quite sick without adequate electrolyte studies beforehand.

CASE 6 (S.H. A7106). A 68-year-old man entered the hospital with a severe coronary thrombosis. He also had a Grade 3 benign prostatic hypertrophy and urinary retention. The cardiac condition was treated in the usual manner, including a low-salt diet, and the urinary retention was treated with an inlying urethral catheter. At the end of 6 weeks the heart condition appeared sufficiently improved to warrant some more definitive treatment of the prostatic obstruction. As part of the preparation for this operation the blood sodium level was determined and found to be only 131 milliequiv. per liter. Accordingly, the salt restriction was removed, and the blood level allowed to rise to 136 milliequiv. per liter before the operation was scheduled.

CONCLUSIONS

Hyponatremia is not uncommon in urologic patients and may be a very serious complication. It is particularly likely to develop in patients who have had long-standing chronic urinary-tract obstruction, and should be considered in all patients who have been on a low-salt diet. Azotemia and dehydration, especially if associated with an adequate fluid intake and output, suggest the possibility of sodium depletion. It should be possible to make an early clinical diagnosis, and the condition can easily be corrected by the administration of sodium chloride and water.

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MULTIPLE BENIGN CHRONIC GASTRIC ULCERS*

Report of Two Cases Each with Three Simultaneous Ulcers

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PHILADELPHIA

PREOPERATIVE x-ray demonstration of three distinct, chronic gastric ulcers occurring simultaneously in a patient is unique in our experience. The relative rarity of similar cases in the literature prompted us to report the following 2 cases.

CASE REPORTS

CASE 1. In November, 1954, a 45-year-old woman was seen with severe epigastric pain of 1 year's duration. The pain usually followed the noon meal and lasted for a variable time, being relieved by the use of Anacin and codeine tablets. Her physician advised her in vain to limit the use of alcohol and highly seasoned foods. The patient admitted no severe night pain, referred pain to the back, vomiting or gastrointestinal hemorrhage. Her weight had dropped from 147 to 123 pounds in the previous year.

Physical examination revealed a well developed, somewhat depleted, normotensive woman with mild epigastric tenderness. X-ray study on October 16 clearly showed 3 gastric ulcers. A fractional gastric analysis disclosed a peak value of 37 units of free hydrochloric acid and 55 units of total acid. The hemoglobin, red-cell count, white-cell count and differential, fasting blood sugar and blood urea nitrogen were normal, and a serologic test for syphilis and urinalysis were negative.

At operation on December 1 a large mass was found that involved the posterior gastric wall, which was adherent to

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the posterior half of the body of the pancreas. Palpation through the anterior gastric wall revealed a large ulcer crater in the mass. Two smaller craters were found in the lower portion of the posterior wall of the stomach, 1 near the greater and 1 near the lesser curvature. Three fourths of the stomach was removed, and an anastomosis completed between the gastric stump and jejunum, a modified anterior Polya–Hofmeister procedure being used.

The patient made an uncomplicated recovery from the operation and was discharged from the hospital on December 13. Gross examination of the resected stomach revealed three gastric ulcers (Fig. 1). The most distal ulcer, which straddled the pylorus near the lesser curvature, was 1 cm. in diameter and 0.3 cm. in depth. The middle ulcer, 3.5 cm. proximal to the pylorus on the posterior gastric wall, also measured 1 cm. in diameter and 0.3 cm. in depth. Mucosal folds radiated from the middle ulcer (Fig. 2); 7 cm. proximal to the pylorus, on the posterior gastric wall, the largest ulcer was 2 cm. in diameter and 1.5 cm. deep. The muscle

FIGURE 1. *Gross Specimen Removed at Operation in Case 1, Showing Three Gastric Ulcers.*

tissue in the base of the ulcer was replaced by fibrous tissue. Microscopical examination of each ulcer showed a characteristically benign appearance. The most distal portion of the ulcer straddling the pylorus contained Brunner's glands at the ulcer margin.

CASE 2. A 45-year-old woman was admitted to the Graduate Hospital on October 22, 1951, with intermittent midepigastric pain of 2 months' duration. The pain tended to radiate posteriorly to the back and was relieved by the ingestion of food and made worse by excitement and whiskey, of which she took liberal amounts. She noted no nausea, vomiting or evidence of gastrointestinal hemorrhage.

Physical examination showed no abdominal tenderness. X-ray study of the stomach and duodenum demonstrated 3 moderate-sized projections arising from the greater-curvature region of the gastric antrum. A fractional gastric analysis disclosed a peak value of 34 units of free hydrochloric acid and 49 units of total acid at 60 minutes.

On October 26 subtotal gastric resection was done, an anterior Polya–Hofmeister procedure being used. Grossly, the resected specimen showed 3 ulcers. Five centimeters proximal to the pylorus a clear-cut oval ulcer on the greater curvature measured 1.2 cm. in its greater diameter; 1 cm. distal to that ulcer was a similar one 0.9 cm. in diameter. The ulcer on the pylorus measured 0.4 cm. in diameter. Microscopically, the three ulcers were benign. No gastritis was present.

DISCUSSION

Multiple small acute erosions and ulcers of the stomach are frequently noted at autopsy and in resected stomachs. In some cases the ulcerations represent an extension of an acute erosive gastritis. Tashkiran[1] reported a row of 32 ulcers in the antrum, ranging from the size of a lentil to that of a dime.

Discrete multiple chronic gastric ulcers are relatively uncommon. They may occur in the stomach alone, in combination with duodenal-ulcer disease or in association with gastric neoplasms. Autopsy specimens and resected stomachs provide the material for most of the cases described in the literature. Cases of three gastric ulcers demonstrated roentgenographically and subsequently proved at operation are very rare.

Bockus[2] reported a case in which x-ray study showed three ulcers on the lesser curvature of the stomach. The ulcers disappeared on medical therapy without surgery.

Of 1000 cases of gastric ulcer at the Lahey Clinic[3] x-ray examination of the stomach was performed in 963. Benign gastric ulcer was diagnosed in 879 cases, of which 21 showed multiple ulcers. Of 84 patients with malignant gastric ulcer, only 1 had more than one ulcer. The authors did not record the number of cases in which three gastric ulcers occurred.

Of 1552 consecutive surgical gastric specimens at the Mayo Clinic[4] 721 represented benign gastric ulcers, and 831 malignant gastric lesions. Multiple

FIGURE 2. *Middle Gastric Ulcer in Case 1.*

ulcers were present in 157 (21.9 per cent) of 721 benign ulcers; however, more than one chronic active ulcer occurred in only 19 cases, of which only 6 showed three or more ulcers. Multiple malignant ulcers occurred in 28 (5.6 per cent) of 660 cases of malignant gastric ulcer.

Russell, Weintraub and Temple[5] reported triple gastric ulcers only once in 405 cases of benign gastric and pyloric ulcer studied roentgenographically.

Welch and Allen[6] described 512 cases of gastric ulcer at the Massachusetts General Hospital during the ten-year period from 1938 to 1947. In 8 per cent of the cases multiple gastric ulcers were found. Four distinct ulcers were present in 1. Portis and Jaffe[7] studied 9171 consecutive autopsies at Cook County Hospital, of which 457 represented all types of peptic lesions. Of 120 cases in which peptic ulcer

was the essential lesion, there were only 3 cases of multiple chronic gastric ulcers.

Buckstein[8] cites a case with x-ray demonstration of two gastric ulcers and one duodenal ulcer confirmed at operation. Shanks and Kerley[9] have no illustrations of multiple gastric ulcers in their textbook. Feldman[10] reported 112 cases of benign gastric ulceration without citing any cases of multiple gastric ulcers. In Case's translation of the book by Shinz et al.[11] it is stated that multiple gastric ulcers are not rare, but no statistics are cited. The same authors[12] present an x-ray film of two large callous ulcer niches on the lesser curvature and posterior gastric wall.

Raffensperger[13] described a case of multiple gastric ulcers after phenylbutazone therapy.

Brown and Intriere[14] reported 2 cases of multiple benign ulcers on the greater curvature, 1 with two, and the other with four ulcers. In neither case did preoperative x-ray study reveal the presence of multiple gastric ulcers.

Summary and Conclusions

Two cases each with three benign gastric ulcers, roentgenographically demonstrated preoperatively, that responded well to subtotal gastric resection are reported. One case represented the additional rare occurrence of three ulcers on the greater curvature of the stomach.

Well authenticated cases of triple gastric ulcers with adequate preoperative x-ray demonstration of the defects are rare in the literature.

The literature is briefly reviewed to indicate the comparative rarity of tripie benign chronic gastric ulcers.

We are indebted to Dr. David Finkelstein for permission to report Case 2 and to Dr. Valdes DaPena for the photographs of the resected stomach.

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MEDICAL PROGRESS

THE HUMAN HEMOGLOBINS IN HEALTH AND DISEASE (Continued)*

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Fetal Hemoglobin in Normal and Pathologic Conditions

Although fetal hemoglobin has been recognized since 1866[19] its occurrence in normal and pathologic states has been extensively investigated only during the past few years.[20,30,73,114,116-125] Hgb F appears at the time red cells are first developed in the fetus and is probably the only type of blood pigment present until Hgb A production starts at about the fifth or sixth intrauterine month. At birth 55 to 85 per cent of the hemoglobin is in the embryonic form, after which there is a rapid decrease to normal adult levels[120] (Fig. 6). Contrary to numerous reports in the literature[29,31,67,68,70,126,127] Hgb F does not disappear between the fourth and the seventh month of extrauterine life but is produced in small amounts for variable periods up to the third or fourth year of age.[73,120] Indeed, there is evidence that the mechanism for Hgb F production never ceases completely but continues into adulthood, producing extremely small quantities of the fetal compound.[128] Under normal conditions less than 15 per cent of the hemoglobin is of the fetal variety at the end of the first year of life, although many children at this age will have developed the adult pattern of 99+ per cent Hgb A.[120] No normal child over the age of twenty months has been observed with more than 5 per cent Hgb F. Since the alkali denaturation test for the fetal pigment is insensitive to quantities of less than approximately 2 per cent fetal hemoglobin a normal value by this procedure is to be expected in all healthy children after the age of four.[20,120]

It is generally assumed that Hgb A is the sole type of hemoglobin produced in the normal adult. How-

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Some of the studies reviewed were supported by Grant No. A-640 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Maryland, and grants provided by the China Medical Board and the Mark A. Edison Memorial Fund.

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ever, immunologic evidence,[128] as well as evidence from solubility studies,[5,32-34] indicates that small quantities of Hgb F are also produced by the mature human being. Examination of blood specimens from approximately 200 normal persons indicated that up to 0.65 per cent of the hemoglobin mass is in the fetal form.[128,129] This study was carried out with the use of specific antifetal hemoglobin serums sensitive to the small amounts involved. It is of some academic interest that the mechanism for Hgb F formation, whatever it may be, is not totally lost since under certain pathologic conditions the production of Hgb F appears to be reactivated.[20,126,128] Furthermore,

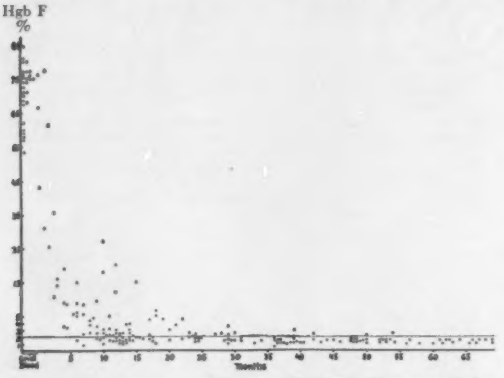


FIGURE 6. *Scattergram, Showing Hgb F in Newborn Infants and Children (Reproduced from Chernoff and Singer[129] with the Permission of the Publishers).*

The horizontal line at 2 per cent represents the upper limit of values obtained in normal adults. Figures above this line represent concentrations of Hgb F.

Hgb F seems to be under the genetic control of a set of alleles different from those determining the other hemoglobin types.[89-91] It is unlikely that a genetic mechanism would cease to function completely at an early age, only to manifest itself once again under the influence of severe stress phenomena. One might postulate, however, that the mechanism for Hgb F production is always present but that normally its expressivity is so interfered with, either by other types of hemoglobin or by genetic modifiers, that only minute quantities are produced.[89] In the hematologic disorders characterized by abnormal amounts of Hgb F these modifiers may lose to some extent their ability to suppress Hgb F formation, or other factors may act to increase the expressivity of the fetal pigment.

A number of the hereditary hemoglobin syndromes are characterized by the production of fetal hemoglobin throughout the natural history of the disease.[5,20,30,73,81,82,113,114,116-121,125,130,131] Chief among these are the major thalassemia syndromes and sickle-cell anemia. In the former, up to 90 per cent of the hemoglobin may be of a type indistinguishable from normal Hgb F.[20,73,82,113,114,130,132] Indeed, in my experience, the few patients with Cooley's anemia who have failed to show an increased concentration of Hgb F have had other atypical features associated with their disease, such as erythrocytic inclusion bodies[132-135] or the absence of thalassemia in one or both parents.[134] In the less severe major thalassemia syndromes smaller amounts of Hgb F may be detected, and in the minor forms of the disease, normal or only minimally elevated values for Hgb F are encountered.[20,73,114] In thalassemia trait the hemoglobin pattern as determined by electrophoresis and alkali denaturation is within normal limits.[20,30,73,96] Thus, the quantity of Hgb F parallels, roughly, the clinical and hematologic severity of the thalassemia states.

Patients with sickle-cell anemia, in almost all cases, demonstrate an increased concentration of Hgb F.[20,-128] Values of up to 40 per cent Hgb F have been found.[136] No correlation exists between the severity of the clinical or hematologic manifestations and the amount of the fetal compound.[20] No spontaneous alterations in the percentage of Hgb F have been detected concomitant with the changing status of the patient. Of the few patients with sickle-cell anemia who do not have increased values for Hgb F, the majority are examples of one of the sickle-cell variants, particularly sickle cell-Hgb C disease.[8,92,106] Persons with the sickle-cell trait do not have increased amounts of the embryonic compounds.[20] In the remaining hereditary hemolytic anemias due to the abnormal hemoglobins one usually finds small to moderate amounts of Hgb F, as will be described subsequently.

Hereditary spherocytosis is probably not a disease related to a specific hemoglobin abnormality. Only about a third of the cases display an increased quantity of Hgb F.[20,128] In most of those with elevated values, concentrations of less than 10 per cent Hgb F are usually found, although 1 child has been observed with as high as 20 per cent Hgb F.[20] It seems likely that the basic problem in this disease is the production of defective stroma under the control of an abnormal genetic mechanism.[137] The presence of Hgb F in this disease may therefore be the result of chronic stress to the bone marrow, similar to that which occurs in the acquired hematologic disorders described below.

In addition to the elevated quantities of Hgb F observed in the hematologic diseases due to the genetically determined abnormalities of hemoglobin synthesis, the amount of the embryonic pigment may also be increased in some acquired hematologic disorders in which the bone marrow is under prolonged, severe stress.[20] Included in this group are chronic leukemias, metastatic carcinoma to the bone marrow, myeloma and pernicious anemia. In a small percentage of such patients the quantity of Hgb F will be elevated, probably as a result of increased activity of the genetic mechanism determining its production. Rarely is this increase greater than 10 per cent of the total hemoglobin mass, although as much as 50 per cent Hgb F has been observed in 1 case of Di Guglielmo's disease.[124]

Normal values for Hgb F are found in most other

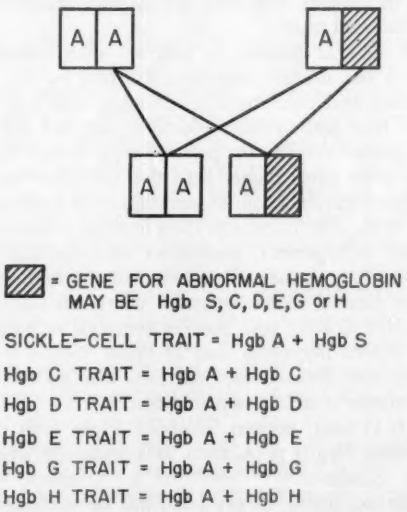
hematologic disorders such as iron-deficiency anemia and acquired hemolytic anemia.[20,128] The alkali denaturation procedure may at times, therefore, prove a useful, though nonspecific, test in distinguishing one of the more severe thalassemia states from iron-deficiency anemia and sickle-cell anemia from sickle-cell trait complicated by a superimposed anemia, as well as the hereditary from the acquired hemolytic anemias.

Hematologic Syndromes Due to Abnormal Hemoglobins

With the multiplicity of human hemoglobin forms now recognized, the variety of clinical syndromes that may result is limited only by the number of permutations and combinations of the hemoglobin types. To these must be added the syndromes consisting of an abnormal hemoglobin combined with one of the hereditary hematologic defects such as thalassemia and hereditary spherocytosis. To systematize the knowledge in this field, therefore, the hemoglobin syndromes are divided on the basis of genetic considerations, and the salient features of each syndrome are discussed.

Heterozygous Hemoglobin-Trait Syndromes

The heterozygous hemoglobin-trait syndromes are hematologic conditions in which the gene for an abnormal hemoglobin replaces one of the two allelomorphs determining Hgb A. The patient is therefore heterozygous for both Hgb A and the abnormal pigment. Hgb A comprises over 50 per cent of the total hemoglobin when quantitative determinations are carried out, for reasons postulated in the previous section. Similarly, Hgb F is present only in trace quantities. In the absence of any data suggesting spontaneous mutations, the usual mode of inheritance may be schematically represented as in Figure 7, in which one parent is seen to transmit the gene for Hgb A, and the other for one of the abnormal hemoglobins.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= GENE FOR ABNORMAL HEMOGLOBIN
MAY BE Hgb S, C, D, E, G or H
SICKLE–CELL TRAIT = Hgb A + Hgb S
Hgb C TRAIT = Hgb A + Hgb C
Hgb D TRAIT = Hgb A + Hgb D
Hgb E TRAIT = Hgb A + Hgb E
Hgb G TRAIT = Hgb A + Hgb G
Hgb H TRAIT = Hgb A + Hgb H

Figure 7. *Schematic Representation of the Hereditary Aspects of the Heterozygous Hemoglobin Traits.*

At present six hemoglobin traits have been recognized. These are sickle-cell trait (Hgb S trait) and Hgbs C, D, E, G and H traits. Contrasting features of note are listed in Table 4.

Sickle-cell trait is a benign condition characterized primarily by the ability of the erythrocytes to undergo sickling, the phenomenon that results from the crystallization within the cell of insoluble reduced Hgb S.[50] The trait occurs in 7 to 9 per cent of Americans Negroes[6,7] although a prevalence of up to 45 per cent has been detected in some African tribes.[90,98-101,-138-146] The limitation of Hgb S to persons of Negro blood seems so definite that some investigators have stated emphatically that the presence of sickling is undeniable proof of Negro ancestry.[147,148] Occasional reports of sickle-cell disease in Caucasians almost invariably come from areas where admixture with Negro blood is quite likely. In the few reports in which such an admixture seems more remote, adequate family studies have not been carried out to exclude this possibility. Extensive studies by Lehmann[90] and others[139,149-151] suggest that the sickling tendency may have arisen as a mutation in the inhabitants of Southern Arabia[142a] or in the Veddoid inhabitants of Southern India and have been transported to Africa and subsequently to the Mediterranean area and the Americas through invasion, the use of African mercenaries and the slave trade. Isolated foci of the sickle-cell trait in such areas as central Greece[152] could well have arisen as a result of spontaneous mutations. Nevertheless, it would be difficult to exclude the possibility that this genetic defect was introduced into these regions by miscegenation with African natives known to have visited the lands along the Mediterranean Sea over two thousand years ago.

Table 4. *The Heterozygous Hemoglobin Traits.*

Trait	Hgb Types	Prevalence	Sickling	Anemia	Red Cell Constants	Target Cells
						%
Sickle-cell trait	A+S	7-9% of American Negroes	+	–	Normal	4
Hgb C trait	A+C	2% of American Negroes	–	–	Normal	0-40 (Average, 20)
Hgb D trait	A+D	Caucasians (rare)	–	–	Normal	?
Hgb E trait	A+E	13% of Thais	–	–	Normal	2
Hgb G trait	A+G	No racial distribution	–	–	Normal	?
Hgb H trait	A+H	Very rare	–	–	Normal	<2

Except for the sickling tendency no specific clinical, hematologic or physical abnormalities are believed to be associated with this syndrome. Recently, however, it has become apparent that the benignity of the sickle-cell trait may have to be re-evaluated since at least two complications, hematuria and splenic infarction, may develop in such patients. From the hematologic standpoint target cells comprise less than 4 per cent of the total erythrocytes on the stained blood film.[106] The corpuscular constants (mean corpuscular volume and mean corpuscular hemoglobin concentration) are normal, as are the osmotic and mechanical fragilities. Survival time of the red cells, determined by several technics, has been uniformly normal.[153-155] Hemoglobin analysis reveals a pattern of Hgb A plus Hgb S, the latter pigment comprising 22 to 46 per cent of the total hemoglobin mass[1,107,108] (Fig. 5). Hgb F is present in normal amounts[20] (Table 3).

Hematuria is frequently observed in patients with true sickle-cell anemia and its variants.[6,7,156] Its occurrence in patients with sickle-cell trait, however, was not recognized until the description by Abel and Brown[157] in 1948. Since then, idiopathic hematuria in patients with sickle-cell trait has been reported in the literature in approximately 25 cases.[158-165] In addition to the above examples of hematuria, 7 cases have been seen in this clinic during the past two years, and I know of at least 25 other patients in whom this complication has developed. The use of precise methods for diagnosing hematologic diseases on the basis of their hemoglobin types, however, has indicated that some of the reported cases represent variants of sickle-cell anemia and not examples of the trait. Thus, a review[8] of 4 of the 7 patients described by Goodwin et al.[159] demonstrated that 2 have sickle-cell trait, 1 is an example of sickle cell-Hgb C disease and 1 has sickle-cell anemia. Nevertheless, although some of the reported cases have been erroneously classified, there can be no doubt that a significant number of persons with well documented sickle-cell trait have severe unexplained hematuria. Examination of kidney sections from specimens removed at nephrectomy have shown dilated renal and pelvic arterioles, capillaries and sinusoids, particularly in the submucosa of the edematous papillae.[162,163] The engorged vascular channels are usually filled with agglomerates of sickled erythrocytes. These findings are believed to result from local anoxia, which causes sickling of the erythrocytes,[166] stasis and the establishment of a vicious circle leading to ischemia, necrosis and hemorrhage. Because the majority of cases of hematuria involve the left kidney several investigators have postulated that an anatomic or structural predisposition exists in this kidney. That both kidneys are vulnerable, however, cannot be denied since several patients have had right-sided or bilateral involvement.

Reports of splenic infarction occurring in persons with the sickle-cell trait flying at moderate altitudes in both commercial and military airplanes have aroused considerable interest. During World War II, Henderson and Thornell[167] studied the effect of high-altitude flying in patients with both sickle-cell anemia and sickle-cell trait. There was no apparent increase in intravenous sickling or the development of any symptomatology in the 4 subjects with the trait at an elevation of 10,000 feet. Findlay et al.[168] found only a slight increase of sickling in 3 subjects at 15,000 feet, again without the development of any symptoms. Nevertheless, approximately 30 cases have now been reported in which nonanemic persons with sickle-cell trait, flying at altitudes of 4,000 to 15,000 feet, have had severe left-upper-quadrant pain and probable splenic infarction.[169-178] In the absence of electrophoretic studies of the hemoglobin patterns in many of these cases it is difficult to be certain that all are examples of the sickle-cell trait. This is especially important in view of the observations of Motulsky et al.,[173,179] who found that of 6 cases of splenic infarction in patients believed to have sickle-cell trait, 2 were actually examples of sickle cell-Hgb C disease, and 1 an example of thalassemia-Hgb S disease; only 3 patients had the pattern of sickle-cell trait. Recently, Smith and Conley[178] reviewed 15 other cases and found sickle-cell trait in 11, sickle cell-Hgb C disease in 3 and probable thalassemia-Hgb S in 1. As with the problem of hematuria, however, there can be no doubt that splenic infarction occasionally takes place in persons with well documented diagnoses of the sickle-cell trait.

The clinical pattern in patients with splenic infarction has usually been characterized by the onset of nausea and vomiting and left-upper-quadrant pain two to four hours after the patient becomes airborne. The critical altitude for patients with sickle-cell trait seems to be much higher than that for those with the sickle-cell variants, an observation that may be related to the dynamics of sickling in these conditions.[154] Splenic enlargement, sometimes of remarkable degree, rapidly ensues. The hematologic findings are usually limited to an increased white-cell count and a positive sickling test. Spleens removed at operation have shown numerous and at times massive hemorrhages and infarctions, with the sinusoids packed with masses of sickled erythrocytes.

Hgb C trait, present in about 2 per cent of the American Negro population, is a clinically asymptomatic condition.[55,56,76,92,106,110,180] A much higher prevalence, up to 15 per cent, has been observed in some areas of west central Africa.[181,182] Reports from Algeria and the Cape Town area indicate its occurrence in those regions as well.[183-185] The hematologic findings are entirely within normal limits, except for the appearance of increased numbers of target cells and very mild hypochromia of the red cells.[55,76,106] (Table 4). Target cells range in quantity from 0 to 40 per cent, with an average of approximately 20 per cent.[56,76,92,106,180] There is no apparent relation between the number of target cells and the amount of

Hgb C present in the erythrocytes.[106] Indeed, some of the highest percentages in Hgb C have been observed in persons whose blood films failed to show target cells. The observation has been made that the number of target cells is strikingly uniform in any given family group.[106] This finding suggests that another genetic mechanism, unrelated to Hgb C per se, may be operating to determine the percentage of drome except for the electrophoretically distinct hemoglobin.

Hgb E trait, found in approximately 13 per cent of the Thai population,[187,188] has also been observed in the Veddas of Ceylon[189] and in about 6 per cent of Indonesians in Jakarta.[190] There are no reports of its occurrence in other parts of the world. This observation is of great anthropologic interest in view

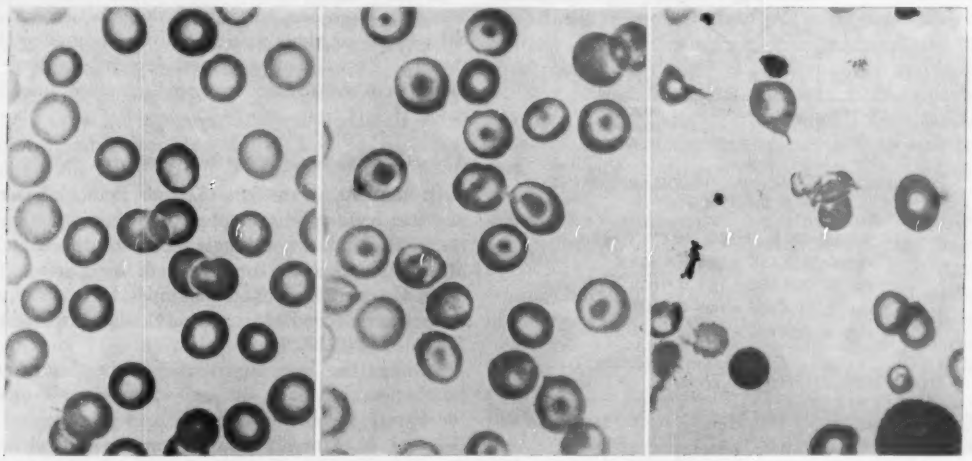

FIGURE 8. *Photomicrographs of Blood Films from the Hgb E Syndromes (X 1150). From left to right, Hgb E trait, homozygous Hgb E disease and thalassemia-Hgb E disease.*

target cells. In persons with the greatest quantity of leptocytes the osmotic fragility of the erythrocytes is usually somewhat decreased. Despite the apparent hypochromia of the red cells on the stained blood film, the mean corpuscular volume and the mean corpuscular hemoglobin concentration in the Hgb C trait are within normal limits, suggesting that the erythrocytes are thinner than normal and so give the impression of hypochromia.[55] Sickling is absent. There is no evidence of a hemolytic process. The survival time of Hgb C trait red cells, originally reported to be prolonged,[180] has now been demonstrated to be within normal limits both by the Ashby technic and by the chromium-51 method.[106,155] Hemoglobin analysis reveals the pattern of Hgb A plus Hgb C. The latter compound comprises from 28 to 44 per cent of the total, with most examples falling within the range of 32 to 35 per cent Hgb C.[55,56,79,106,110] Fetal hemoglobin is present in normal amounts (Table 3).

Hgb D trait has been observed in only two kinships: one in a Caucasian family originating in midwestern United States,[11] and the other in a white family in Europe.[186] The pattern of Hgb A plus Hgb D with normal amounts of Hgb F is seen. Electrophoretically, Hgb D trait cannot be distinguished from Hgb S trait.[11] The absence of sickling and the high solubility of the hemoglobin in the Hgb D trait permit their easy separation, however. As far as is known, no abnormality is associated with this syn-

of the somewhat similar racial backgrounds of the people showing Hgb E, many of whom are believed to have originated in North China and to have been driven southward in successive waves into their present homelands.[191] Hgb E has not been detected in

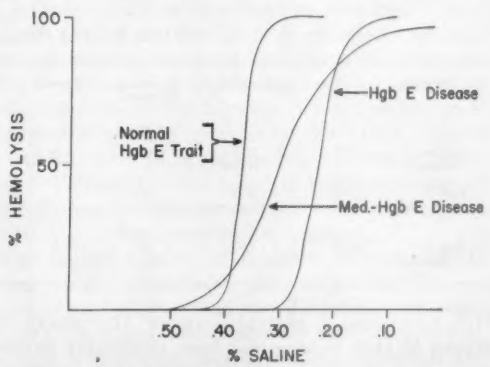

FIGURE 9. *Typical Osmotic Fragility Curves Observed in the Hgb E Syndromes.*

over 200 pure Chinese living in Thailand.[188] The clinical, hematologic and physical findings in subjects with the Hgb E trait are entirely normal, unless complicated by incidental pathologic states.[109,192] Target-cell counts, red-cell morphology (Fig. 8) and constants, fragility tests (Fig. 9) and survival-time

studies[193] indicate no abnormality.[100] The pattern of Hgb A plus Hgb E is seen on paper electrophoresis with the normal adult hemoglobin comprising over 50 per cent of the total blood pigment. The quantity of Hgb F is within normal limits.

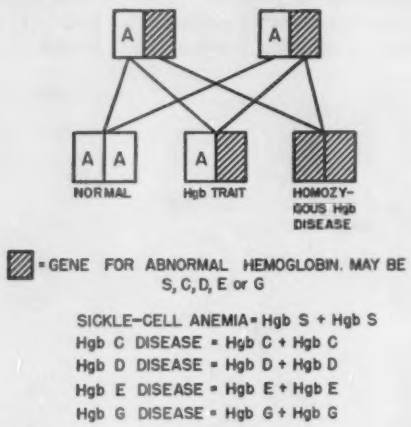
A
A
A A
NORMAL
A
Hgb TRAIT
HOMOZY-
GOUS Hgb
DISEASE
= GENE FOR ABNORMAL HEMOGLOBIN. MAY BE
S, C, D, E or G
SICKLE-CELL ANEMIA = Hgb S + Hgb S
Hgb C DISEASE = Hgb C + Hgb C
Hgb D DISEASE = Hgb D + Hgb D
Hgb E DISEASE = Hgb E + Hgb E
Hgb G DISEASE = Hgb G + Hgb G

FIGURE 10. *Schematic Representation of the Hereditary Aspects of the Homozygous Hemoglobin Diseases.*

Only 2 examples of the Hgb G trait have been recorded. The first of these was reported by Edington and Lehmann[59] in a Negro from West Africa, and the second by Schwartz and Spaet[60] in a white family in California. The abnormal pigment observed by Battle and Lewis[61] and an abnormal hemoglobin detected in a patient in Thailand may also be examples of Hgb G.[62] The clinical manifestations have not been adequately described, but Schwartz[194] reports that patients with the Hgb G trait are asymptomatic except for the presence of the pathologic pigment. Hgb F is found in normal amounts. The genetic relations of Hgb G have not been thoroughly worked out, although the gene controlling this compound is assumed to be an allele of the normal adult hemoglobin. Studies still in progress in the family observed by Schwartz and Spaet[194] raise the question whether Hgb G may be independently transmitted. The paucity of Hgb G carriers and the difficulty of identifying this hemoglobin with technics now available, however, make it unlikely that this question will be answered in the near future.

Hgb H trait, detected by Page, Rucknagel and Jensen[63] in 3 generations of 1 Negro family, appears to be unassociated with any symptomatology. The studies of these investigators revealed that the mother, 4 of her children and 1 grandchild were heterozygous for Hgb H whereas all other members of the family had only Hgb A.[64] The 2 Chinese patients with the combination of Hgb A and Hgb H, described by Rigas et al.,[65] apparently suffer from a severe thalassemialike syndrome. Since both the genetic and clinical aspects of these patients differ so greatly from those of Page, Rucknagel and Jensen[63] it seems unlikely that the former represent cases of uncomplicated Hgb H trait.

The Homozygous Hemoglobin Diseases

In contrast to the heterozygous hemoglobin traits are the homozygous hemoglobin diseases, in which the person inherits a single gene for the same abnormal hemoglobin from each of his parents (Fig. 10). Three well defined examples from this group have been studied extensively. Comparative features are listed in Table 5.

Perhaps the best known disease in this group is homozygous Hgb S disease, or sickle-cell anemia. Sickle-cell anemia occurs in approximately 1:600 Negroes in America and in varying prevalence in Europe and Africa.[90,99-102,138,140,141,142a,152,195,196] Such clinical manifestations as fatigability, jaundice, repeated abdominal, muscle and joint crises, leg ulcers, retarded growth, sexual immaturity and absence of splenomegaly have been described so adequately by others that they need not be repeated here.[6,7] The hematologic findings are those of a chronic normochromic normocytic anemia with elevated reticulocyte count, increased serum bilirubin, increased urobilinogen excretion and elevated hemolytic index. The erythrocytes on the blood film are characterized by polychromasia, sickled cells, 5 to 30 per cent target cells[106] and variable numbers of nucleated red cells. Anisocytosis, poikilocytosis, hypochromia and basophilic stippling are infrequently observed and are not usually found in this syndrome. The osmotic fragility is usually somewhat decreased whereas the mechanical fragility is increased. The bone marrow is almost constantly hyperplastic and exhibits marked erythrocytic stimulation except during phases of

TABLE 5. *The Homozygous Hemoglobin Diseases.*

DISEASE	HGB TYPES	PREVALENCE	CLINICAL SEVERITY	CRISES	SPLENOMEGALY	SEVERITY OF ANEMIA	RED-CELL CONSTANTS	TARGET CELLS
								%
Sickle-cell anemia	S+S	1 : 600 Negroes	+++	+++	Absent	+++	Normocytic normochromic	5-30
Hgb C disease	C+C	1 : 6000 Negroes	+	−	++	±	Slightly microcytic normochromic	40-100 (average, 60)
Hgb E disease	E+E	1 : 250 Thais	+	−	±	±	Microcytic normochromic	25-60

aplastic crisis. The hemolytic nature of sickle-cell anemia is also demonstrable by means of survival-time studies of the erythrocytes, which indicate the presence of an intracorpuscular hemolytic mechanism.[153-155]

Hemoglobin analysis, utilizing the technics of electrophoresis and alkali denaturation, reveals the presence of 60.2 to 99 per cent Hgb S whereas the remainder is Hgb F[3,20,107,136,197] (Fig. 4 and Table 3). As suggested above, Hgb S appears to have less of an inhibitory effect than Hgb A on the expressivity of Hgb F. Although as much as 39 per cent Hgb F has been reported in this disease[136] none of the patients over three years of age seen in our own clinics have had more than 24 per cent Hgb F, and the majority fall within the range of 4 to 10 per cent for the fetal pigment.[20,128] Less than 3 per cent of patients homozygous for Hgb S have a normal amount of Hgb F. Most patients stated to have normal quantities of Hgb F have been demonstrated, on more thorough examination, to be examples of one of the variants of sickle-cell disease. The remainder appear to be homozygous for Hgb S, but often exhibit one or more atypical features in either the clinical or the hematologic aspects of their disease, suggesting that these cases, too, form variants of true sickle-cell anemia.[134] Studies to throw some additional light on this problem are now in progress in a number of laboratories.

Differentiation of sickle-cell trait and sickle-cell anemia usually presents no difficulty. At times, however, patients with sickle-cell trait have severe anemias, hemolytic and nonhemolytic, unrelated to their genetic hemoglobin abnormality, which may complicate the clinical and hematologic findings. Unfortunately, the percentage of sickling elicited by sodium metabisulfite does not help differentiate these two conditions since, in both, 100 per cent sickling is to be expected.[198] However, a number of procedures may be employed to distinguish patients with sickle-cell anemia from those with the trait and an associated anemia. In sickle-cell anemia, sickled cells may be seen on the stained blood film although their absence does not rule out this disease. Sickled erythrocytes are most unusual in the blood film of persons with the trait. The Sherman[199] test, which determines the percentage of sickled erythrocytes in venous blood, can often be utilized to distinguish these two conditions. In homozygous Hgb S disease 25 per cent or more sickled cells are present whereas in sickle-cell trait less than 5 per cent are in this form. Survival-time studies indicating an intracorpuscular erythrocytic defect support a diagnosis of sickle-cell anemia.[153,154] An elevated percentage of Hgb F, although a nonspecific test, suggests the presence of sickle-cell anemia rather than sickle-cell trait.[20] Finally, paper electrophoretic studies reveal a pattern of Hgb S with small amounts of Hgb F in sickle-cell anemia and of Hgb A plus Hgb S in the trait.

The crises reported in patients with sickle-cell anemia have been the source of considerable confusion. Crises may be of 3 basic types, only 2 of which are consistently associated with hematologic changes. The usual type of crisis, with abdominal, muscle and joint pains, is unaccompanied by significant alterations in the red-cell elements of the patient. The degree of icterus may be even less marked during this stage of the disease than in quiescent periods, and no evidence of increased hemolytic activity during such crises has ever been presented.[200] Such an event may therefore be referred to as a clinical crisis. In contrast are the hematologic crises, both aplastic and hyperplastic. Although the hyperplastic crisis, in which a severe increase in hemolytic activity occurs, is a theoretical possibility it is doubtful whether such an event ever actually takes place in sickle-cell anemia. The aplastic crisis, in which the basic defect is a cessation of red-cell production for periods up to two weeks, manifests itself by a most dramatic drop in erythrocyte, hemoglobin and reticulocyte levels, often in a period of three days or less.[201-204] Acute erythroblastopenia is not limited to sickle-cell anemia but may be seen in any person.[204,205] Only in patients with a hemolytic anemia and severe depression of red-cell survival times, such as exist in sickle-cell anemia, is the dramatic lowering of the red-cell count readily observed.

Homozygous Hgb C disease is a rare condition calculated to occur in approximately 1:6000 American Negroes.[55] At present, 24 cases have been reported in the literature,[55,86,94,110,130,155,206-214] to which 4 more, seen in this clinic, may be added.[134,215] Recently, Diggs et al.[209] studied the interesting case of a white patient with homozygous Hgb C disease whose erythrocytes contained peculiar hemoglobin crystals. Similar crystals were seen in 1 of my Negro patients with Hgb C disease.[134] The occurrence of this disease in a Caucasian suggests that Hgb C need not be limited to the Negro population, although intermingling of the races can never be ruled out with certainty. The high prevalence of admixture with American Indian blood in patients with Hgb C suggested a possible reservoir in this group. Studies by Rucknagel[216] in approximately 150 Southeastern and 100 Plains Indians failed to reveal any case of Hgb C, but further examination of the American Indian population seems to be indicated.

The limited number of examples of pure Hgb C disease present a strikingly uniform pattern. In addition to mild symptoms of easy fatigability and some dyspnea on effort many patients have complained of vague intermittent arthralgias and occasional abdominal pain. True crises, as seen in sickle-cell anemia, have not yet been reported. Jaundice has been inconstant and mild. Gallstones have complicated the course of 2 of the patients in this group.[55,110] The oldest patient studied was fifty-two years of age,[94] but there is no reason to believe that pure Hgb C disease is incompatible with a normal lifespan. Four women have given birth to a total of 15 children, all of whom, as far as can be determined, have had

the hemoglobin formula, Hgb A plus Hgb C, the expected pattern if the mother is homozygous for Hgb C.[55,94,110,215] The spleen is almost always enlarged, except in the youngest age group. Splenomegaly is generally severe, the organ extending 5 cm. or more below the left costal margin in almost all the adults. Hepatomegaly of significant degree was reported in only 2 of the patients of Singer et al.[210] Hematologic examination indicates normal or only slightly decreased hemoglobin and red-cell levels (Table 5). The red cells are slightly microcytic or normocytic, the mean corpuscular volume ranging from 66 to 90 cubic microns. Mean corpuscular hemoglobin concentration determinations fall within the normal values of 34 to 38 per cent. Reticulocyte counts are normal or only slightly increased, except for the remarkable case

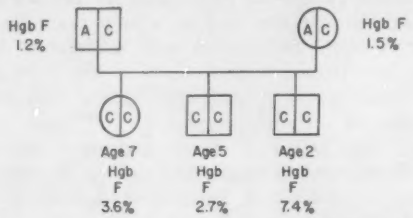

FIGURE 11. *Homozygous Hgb C Disease in 3 Children of a Family in Which Both Parents Have Hgb C Trait.*
All 3 children have homozygous Hgb C disease. (Letters refer to hemoglobin types, which were determined by paper electrophoresis; Hgb F determinations were made by the alkali-denaturation procedure.)

of Diggs and his associates,[209] in which up to 94 per cent of the erythrocytes were reported to be reticulated cells. The blood film is striking primarily for the high numbers of target cells, a morphologic alteration that may at times involve all the erythrocytes.[94] In general, target-cell counts fall within the range of 40 to 90 per cent, with an average of approximately 60 per cent. Poikilocytosis, anisocytosis and hypochromia are not generally present. Small numbers of nucleated red cells are occasionally seen. Sickle cells are absent, and the sickling phenomenon cannot be elicited. The osmotic fragility is invariably decreased to a moderate degree. The mechanical fragility of the erythrocytes, determined in only 5 of the cases, was slightly increased in 2.[55,94,110,207] Bone-marrow examinations reveal moderate erythrocytic hyperplasia. Studies of red-cell survival time, carried out in 4 of the reported cases, indicate the mild hemolytic nature of homozygous Hgb C disease.[110,155,207,210] The cells from the patient of Terry et al.[55] survived for a hundred and six days, a figure that cannot be considered grossly abnormal. The hemolytic index was slightly elevated in the 2 cases in which this determination was carried out.[55,207] Hemoglobin analysis indicates only Hgb C by paper electrophoresis. With the exception of the three-and-a-half-year-old child described by Ranney[94] Hgb F determinations in the reported examples of Hgb C disease have been normal (Table 3). Of the 4 patients seen in this clinic, 3 children had values of up to 7 per cent Hgb F, slightly higher than would be expected for normal children of the same age.[134]

The genetic features of this mild, normochromic, slightly microcytic hemolytic anemia are well illustrated by a family under my own observation, in which each of the 3 children has homozygous Hgb C disease.[215] The parents are examples of the Hgb C trait (Fig. 11).

Homozygous Hgb D disease, theoretically an extremely rare combination, has not yet been encountered clinically.

Homozygous Hgb E disease may be expected to occur in approximately 1:250 Thais. At present, 6 examples of this syndrome have been encountered in patients ranging in age from nineteen to forty years.[109,192] All were in good to fair health although a history of tiredness, easy fatigability and mild arthralgias could usually be elicited. Minimal splenomegaly was present in 2 patients, and the liver edge was just palpable in a third. All looked suggestively icteric although van den Bergh determinations did not support this observation.

Except for 1 patient whose course was complicated by malaria patients with Hgb E disease have had similar hematologic findings. The erythrocyte counts are normal whereas hemoglobin levels are low. Red-cell constants indicate a microcytic normochromic blood picture (Table 5). Mean corpuscular volumes range from 65 to 75 cubic microns, and mean corpuscular hemoglobin concentrations fall between 32 and 35 per cent. Reticulocyte counts are normal. The blood film is characterized by the presence of 25 to 60 per cent target cells, without other morphologic abnormalities. Sickling is absent. Nucleated red cells have not been observed except in the patient with malaria. The resistance of the erythrocytes to saline solutions is strikingly increased and the osmotic-fragility curve is shifted symmetrically to the right (Fig. 9). Hemolysis starts in the tubes with approximately 0.32 per cent saline solution and is completed at concentrations of 0.16 per cent or less. Bone-marrow examinations reveal moderate erythrocytic hyperplasia. Determination of the hemolytic index in 1 case was normal. Although the available evidence does not support the occurrence of accelerated hemolysis in pure Hgb E disease, the data are too fragmentary to exclude the presence of a mild hemolytic component. Paper electrophoresis in these patients demonstrated a single hemoglobin component in the position of Hgb E. Hgb F determination by the alkali-denaturation procedure was normal except in 1 patient, who had a slightly elevated value of 6 per cent.

(To be concluded)

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MEDICAL INTELLIGENCE

CHRONIC SUBDURAL HEMATOMA OF THE SPINAL CORD

Report of a Case

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ALTHOUGH intracranial chronic subdural hematoma is a well recognized and documented clinical entity, the occurrence of such a lesion in a spinal location has not heretofore been reported to my knowledge. The following case is presented as an example of such an occurrence.

CASE REPORT

A 40-year-old oilfield mechanic was admitted to the Medical Center Hospital on February 14, 1955, with a chief complaint of progressive weakness of the right leg of 5 years' duration.

He gave a history of having been injured on February 28, 1950, while working under the floor of an oil derrick that was 5 feet off the ground. At the time of injury he was engaged in carrying a 120-pound battery under the floor of the derrick. Because of the limited space, he had to walk in a bent-forward position, supporting the battery with both hands by means of short handles attached to each end of it. As he came to a small ditch he extended his left leg to cross it. His right foot suddenly slipped on the wet ground, his left leg flew up into the air, and he fell heavily on his right buttock in a semisitting position, still holding the battery cradled in his lap. He immediately felt "paralyzed from the waist down." There was no one about at the time to help him, and so he lay for approximately 5 minutes unable to move his legs and lower trunk. At the end of this time considerable strength and feeling returned to his left leg, and he was able to pull himself up into a sitting position on a nearby box. After about 30 minutes there was some return of strength in the right leg, and he was able to make his way to his automobile nearby and drive home.

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During the next 3 days there was almost complete return of strength in the left leg. The right leg remained quite weak, however, and he was admitted to the hospital for observation and treatment. X-ray films of the thoracic and lumbar areas of the spine were said to have yielded no evidence of injury. No specific treatment was given, and the patient was released from the hospital in about 2 weeks. It was believed that further recovery had occurred in the right leg during this interval. There was no record of the neurologic findings at this time.

Although he had worked regularly since March, 1950, he had had persistent and continual weakness of the right leg. The weakness had been more pronounced after working, riding, straining and sitting. He had noticed difficulty in initiating micturition, discovering, after a period of trial and error, that if he stood on his right leg, leaning against the wall with his right arm elevated, he was more successful than in any other position. He experienced a similar difficulty in the act of defecation, and frequent enemas eventually became necessary. He also found it impossible to consummate the act of coitus except in a certain stereotyped manner and position, quite different from his previous experience.

Gradually, over the years, he thought that his weakness was becoming more pronounced. He also began to be bothered by severe, throbbing frontal headaches, lasting from several hours to as long as a day or so and becoming steadily more frequent. He discovered accidentally that he could obtain immediate, temporary relief from the headaches by raising his arms over his head and hanging by his hands from some overhead support, such as the top of a door jamb. As soon as he let go, however, the headache immediately recurred, usually with somewhat less intensity. If he repeated this often enough, the headache gradually subsided and with it a sensation of nervous tension that usually accompanied it.

During the past few months he had noticed that if he worked strenuously for an hour or 2, the weakness in the right leg became very severe, so that he realized that something needed to be done before the situation became critical.

He had always been in excellent health, having had no important illnesses or injuries.

Physical examination revealed a well developed, well nourished man of about the stated age who did not appear ill. Station and posture were normal, but he walked with a perceptible limp, favoring the right leg. He was alert, cooperative, oriented and rational. On neurologic examination there was approximately 50 per cent loss of strength in the right leg. The knee and ankle reflexes on the right were markedly increased, with unsustained ankle clonus. The plantar response on the right was strongly extensor. There was approximately 75 per cent loss of perception of vibratory sensation at the right ankle. There was some diminution in pain perception in the entire left lower extremity although a definite line of demarcation could not be demonstrated.

Routine laboratory data were normal.

X-ray examination of the thoracic spine revealed some erosion of the pedicle of the 10th thoracic vertebra on the right side. On the 3d hospital day a Pantopaque myelogram was taken. After introduction of the oil a filling defect was demonstrated at the level of the 10th thoracic vertebra on the right side, extending upward across the lower margin of the 9th thoracic vertebra and downward across the upper margin of the 11th (Fig. 1). The oil flowed past this defect very slowly along the left margin. Examination of the spinal fluid removed before myelography revealed the total protein to be 122 mg. per 100 cc.; the fluid was otherwise normal.

On the 5th hospital day the 11th, 10th and 9th thoracic laminae were resected (in that order). The epidural fat was irregularly distributed over the exposed dura and resembled somewhat, in outline, the defect seen at myelography. On removal of the upper rim of the 10th lamina prominent dural pulsations that had not been present caudally were encountered. The epidural fat was then carefully removed from the dura, revealing an area of bluish discoloration under the dura in the pulsating region. The dura was incised caudal to this level at the 11th segment, and an opening was made into the subarachnoid space, allowing the spinal fluid to run out. The bluish, pulsating area remained unchanged.

The incision in the dura was then carried upward to the 9th thoracic segment. This exposed a sac, filled with fluid, which was not adherent to the undersurface of the dura, judging from the ease with which the edges of the dura were mobilized laterally. The sac bulged outward between the retracted dural margins; it was approximately 2 cm. in length and 1 cm. in width and lay almost entirely posterior and lateral to the right half of the spinal cord, just barely encroaching on the left side at the midline. Its parietal membrane was blue gray and uniformly semiopaque, with a finely wrinkled, parchmentlike texture.

A longitudinal incision was made in this membrane, and approximately 1 cc. of xanthochromic fluid ran out (the total protein of this fluid later was found to be 1250 mg. per 100 cc.). When the parietal membrane was widely opened a saucer-shaped depression of the right half of the spinal cord was exposed, corresponding to the dimensions of the sac, and measuring approximately 5 mm. in depth. The walls of the depression sloped sharply downward from its rim. The visceral layer of the sac was completely transparent, the depressed cord being seen clearly through it. No abnormality in the appearance of the cord was apparent.

The attachment of the opened parietal layer of the sac to the rim of the depression was then gently tested and was found to be firmly adherent. It was therefore deemed prudent not to attempt to remove the sac, because of the possibility of provoking irreversible spinal-cord damage. It was left widely open, however, so as to prevent its reformation. The dura was then closed with a continuous suture, except for a 1-cm. segment directly over the opening in the sac; this was left unapproximated to serve as a decompression and also to reduce the chances of re-formation of the sac. The jugular veins in the neck were then compressed by the anesthetist, and a quick wave of spinal fluid passed downward along the exposed segment of cord. None appeared in the sac or came out through the overlying dural opening. The wound was then closed tightly in layers, without drainage, and the operation terminated.

The postoperative course was uneventful. The patient was ambulatory on the 3d day and discharged on the 7th. One month after operation there was no change in the neurologic findings, but he believed that he was definitely, but not greatly, improved as compared with his preoperative status. He returned to work 8 weeks after the operation.

Discussion

The mechanism of the formation of a chronic hematoma in the spinal canal must be quite different from that occurring intracranially, in which *direct* force is almost always present, with application of stress to the bridging vessels, causing them to tear and bleed. In the spinal location, however, a direct blow sufficient to cause such hemorrhage would usually be fatal; even if it were not, the resultant damage would be so great that the presence of a hematoma would be of only theoretical interest.

It seems, therefore, that these lesions are formed intraspinally on the basis of an *indirect* application

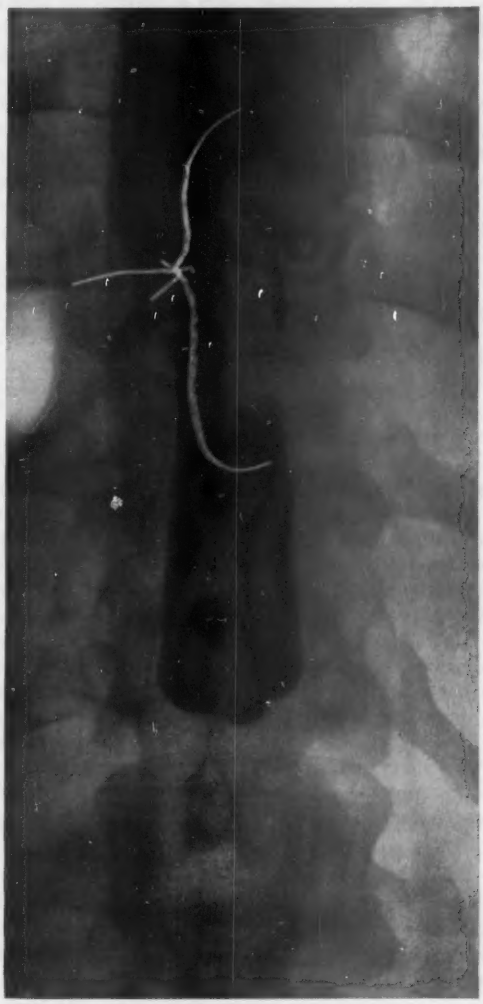

Figure 1. *Myelogram, Showing Filling Defect at the Tenth Thoracic Vertebra on the Right.*

of force, a sudden, great increase in abdominal and thoracic pressures being transmitted intravascularly along the lateral spinal arteries and veins through the intervertebral foramens to the intraspinal segments of these vessels. Such a rapid increase in the intravascular pressure of these vessels as they cross the subdural and subarachnoid spaces would not be neutralized by a simultaneous increase in spinal-fluid pressure because of the shielding effect of the spinal column and its ligaments. For a short but measur-

able interval, therefore, there would be such a great disparity between the intravascular and extravascular pressures that rupture of the vessels would become possible. In the event of such a rupture the resultant bleeding could involve the subdural "space." Such a spinal subdural accumulation of blood would be subject to the same group of forces as governs the formation of fluid collections intracranially; there is the same relation of the meninges, of the spinal fluid and of a rigid, closely applied, bony enclosure.

It is true that most of the lateral spinal vessels are small, but the lateral spinal artery that accompanies the tenth or eleventh anterior thoracic root (artery of Adankewicz) is considerably larger than the others and would be quite likely to cause clinical symptoms if ruptured. The case presented above is probably an example of such an occurrence.

The best treatment of these lesions seems to be wide opening of the parietal layer of the sac, possibly with removal of such a layer. I believe, however, that there should be no attempt to remove the visceral membrane as with cerebral hematomas; such a course would be fraught with danger of injury to a spinal cord already laboring under the strain of a reduced blood supply; this is especially true when much of the cord function is still intact, as in this case. The purpose of surgical exploration, therefore, is, first, to establish the diagnosis and, secondly, to accomplish drainage of the hematoma so as to prevent progression of symptoms and to render re-formation impossible.

Chronic subdural hematoma of the spinal cord must certainly be a rare lesion, but may be more frequent than suspected. Patients with clinical diagnoses of herniated nucleus pulposus, spinal-cord concussion and spinal-cord contusion may fall into this group. With present-day methods of radiologic examination of the spinal canal more of these cases will probably be reported in the future.

Summary

A case of chronic subdural hematoma of the thoracic spinal cord is presented, and its probable mechanism of formation and suggested treatment are discussed.

DOCTORS AFIELD

François Rabelais

Richard Warren, M.D.*

BOSTON

IT is the distinction between a snicker and a laugh that has given Rabelais to the ages. For his was the big honest laugh, the "rire immense" understandable by and irresistible to all men. What is known of the life of this most human of humanists who entered medicine relatively late in life so that he might learn more about man?

He was born at Chinon between 1483 and 1495, and died in 1553, probably at Lyons. It is natural that the details of the life of a man fond himself of the tall story should be so surrounded by legends that facts are now difficult to distinguish from them. His early education is unknown, although tradition states that it was in the local abbey and convent. The first definite record of him is his signature on a deed of purchase made by the monks of the Franciscan Monastery of Fontenay-le-Comte in 1519. To have arrived at the state of responsibility implied by this signature he must have joined the order several years before. It is impossible to discover when it was that he became known as one of the most erudite men of his time. The Franciscan order was notably nonliterary as compared with the Benedictine, and yet it is known that he found there a kindred literary spirit in one Pierre Amy. Together they corresponded with Guillaume Budé, secretary to King Francis I, and one of the foremost of French scholars. It is reported that their books were confiscated, owing, it may be assumed, only to the fact that the young men had become somewhat obnoxious in their virtuosity, since the books were later returned.

A few years later he transferred to the Benedictine Monastery at Maillezais. This most difficult administrative maneuver was arranged for him by Geoffroi d'Estissac, the local bishop, whom Rabelais had known from the old days at Chinon. There is thus, by that time, evidence of his outstanding interest in scholarship and literary matters and his ability to make and keep friends. The latter quality got him out of many scrapes later on, and seems to have been a particularly desirable attribute in that turbulent period of the Renaissance.

He spent five years at Maillezais in the tolerant and enlightened society of the Benedictines. He left there before 1530 to become a secular priest, which would enable him to travel. With only occasional intermissions he was a wanderer for the rest of his life. He visited other friends of his youth who had become influential, the brothers du Bellay at Langey, and thence proceeded to Montpellier, where, having studied medicine for six weeks, he became a bachelor of medicine in November, 1530.

The medical school at Montpellier, having been started in the twelfth century, was the second one founded in Europe. By 1500 it had taken over from its predecessor at Salerno the distinction of being first in importance. Distinguished early graduates were Arnold of Villanova, famed for his critical, inquiring mind and for having applied the term "aqua vitae" to brandy, the Englishmen Gilbertus Angelicus, who made an ointment of puppy fat, and John of Gaddesden, who cured the son of Edward II of

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smallpox by wrapping him in red cloth. Another famous alumnus was Petrus Hispanus, who later became pope. Prominent men on the faculty when Rabelais was there were Jean Scurron, who later became chancellor, and Rondelet, a strong personality and busy practitioner, possibly the Rondiblis of Book III.

After his degree Rabelais stayed on to teach anatomy and to lecture on Hippocrates and Galen. In 1532 he moved to Lyons, where he was made physician to the Hôtel Dieu. While there he edited the "Aphorisms" of Hippocrates, and the "Ars Parva" of Galen. He soon afterward wrote *The Pantagruel,* the idea for which was taken from a chap book of the time and was first published under the anagrammatic name "Alcofibras Nasier." During the next twenty-three years more books appeared, the first book, or *Gargantua,* probably being the second one written in point of time. After having created Pantagruel the author apparently felt the need of giving him proper (or improper) antecedents.

During the twenty years from then until his death "Maître François" traveled four times to Italy in the company of one or the other of the du Bellay brothers. He is known to have been also at Montpellier, Bezier, Narbonne, Castras, Lyons, Metz, Angers, Glatigny, St. Maur and Meudon. Because of the storms created by the assault of his books on the monkish and educational systems of the time, his leaving the monastery and his repeated unavailability, he had his troubles with various constituted authorities. He was repeatedly censored by the Sorbonne. He was removed from the staff of the Hôtel Dieu. His friends, however, served him in good stead. d'Estissac and a letter written by himself to the Pope, "Supplicatio pro Apostasia," got for him a bull of absolution in 1535 that allowed him to return to the Benedictines if he wished and to practice medicine. The Sorbonne, however, was not placated, and the appearance of further books rubbed salt in the wound. Their dedication to influential people, such as that of the fourth book to Monseigneur Odet, Cardinal de Chatillon, and his ability to keep moving, saved him perhaps from the stake, where perished Servetus and Dolet, contemporaries of his who were hardly more unconventional than he.

In 1546 he was given the position of physician to the Town of Metz at 120 livres a year. In 1550 he transferred to the livings of St. Martin de Meudon and St. Christophe du Jambet, from which he resigned in 1553 just before he died. The fifth book, which appeared about ten years later, was probably written by someone else from notes or a rough draft left by Rabelais. There is no record of his private life. Although there is a transitory unauthenticated allusion to a son who died in infancy it is probable that he never married.

There is disagreement about the background of his decision to study medicine (is this not true of every famous doctor?). It was certainly not for money and position. Doctors in those days were not highly regarded. Erasmus, when suffering from a urinary stone, said, "I have abandoned myself to the doctors and the apothecaries, which means the executioners and the vultures." The most probable reason was a mixed academic and humanistic urge. As Gargantua advised Pantagruel, "Carefully consult the works of the Greek, Arabian and Latin physicians, without slighting the Jewish doctors, Talmudists and Cabbalists. By frequent exercises in dissection acquire a perfect knowledge of that other world which is man." This double-barreled adjuration would satisfy Rabelais's two great urges, scholarship and the study of man. To what greater intellectual satisfaction could any doctor aspire?

What kind of doctor was he? As with every imagination-catching character about whom there is little fact many disciplines claim him for their own. The passages on dream interpretation in Book II, Chapters 13 and 14, have been held sufficient evidence that Rabelais was a psychiatrist. Surgeons have claimed that he envisioned, though none maintain he used, the traction windlass and box of Ambroise Paré for fractures. Although he did not make the contribution of a Vesalius or a Paracelsus he was a teacher and intellectual leader. He was one of the first, if not the first, to give courses in gross anatomy on the cadaver. For his authorities he did not pursue either of the two easiest courses — namely, to throw over the ancients entirely or to follow them blindly in the "magister dixit" tradition. He realized that Hippocrates and Galen, having been repeatedly rewritten by Arabic scribes and repeatedly reinterpreted by the ecclesiastical doctors of the Dark Ages, needed a new look before rejection. This his knowledge of Greek and Latin could provide, and he made his greatest medical reputation in lecturing on and interpreting Hippocrates from the original and in editing the "Aphorisms." He emphasized the fact that Hippocrates himself was the first to state that the tradition of the past should be the last thing to guide medical progress. He never tired of inveighing against the errors that could creep into the profession if it depended on roundabout interpretations by the Syrian and Arabic translators and editors. "Thousands of lives could be lost thereby."

For the rest, medically speaking, there is little other than glimpses. These indicate, however, that his reactions to his profession were the same as those of physicians today. He enjoyed laughing at himself, since in the form of Gargantua he advised Pantagruel never to become a doctor, because doctors "smell of enemas." Yet he took time to define the proper bedside manner of keeping the cheerful countenance and avoiding contentious, irritating at-

titudes and talk. He indulged in a layman's type of joke about a doctor's fee in his treatment of Rondiblis (Book III, Chapter 34), against whom he felt some antipathy since he was "persecuted" (who can think but rightly?) by him for a matriculation fee at Montpellier that he had omitted to pay.

Rabelais was extolled by his successor at Meudon as being a kind practitioner who never withheld his services, or even his purse, from the poor, and he was called by Dolet one of the first physicians of France.

His interest in mankind was intuitive, and, although he was too intellectually curious and restless to settle in one place long enough to create a large practice, he realized that much could be done for all kinds of human suffering without any laying on of the hands. His alleged reason for writing his books with their Gargantuan pornographic humor was to make his patients laugh and so to cure them of their ills. Some have said that this reason was merely a *post hoc* excuse to avoid persecution. More probably he wrote them just because he wanted to, and found out later that they could be used for that purpose to good effect.

His contribution has been likened in its complexity to a cathedral that for every saint in a niche must have a gargoyle devil on the roof. The pornographic aspect of the works is apt to fog for modern readers the appreciation of the man himself. It is difficult to take calmly, for example, the imagination and candor with which Gargantua described his researches into the best means of cleansing the perineum after stool, culminating in the use of the neck of a live goose. But, then, one should think of the problems current in the sixteenth century!

The religiosity and highmindedness of Gargantua's letter to Pantagruel (Book II, Chapter 8) must be sincere:

> Set not your heart upon vanity, for this life is a transitory thing, but the word of God endureth forever. Be serviceable to your neighbor, love him as you do yourself. Honor your teachers. Shun the company of all men you would not wish to resemble; receive not in vain the favors God has bestowed upon you.

His was an articulate spirit, which had to drink deeply of the enjoyment of life. He was a figure whom members of the medical profession are glad to include among themselves. He never deserted the profession for literature as other doctors have done. He practiced what he wrote, and his writing was part of his practice.

Bookplate Collection of the Boston Medical Library

6. Bookplate of John W. Farlow, M.D. (1853-1937), eminent laryngologist and inventor of the Farlow snare and librarian of the Boston Medical Library (1905-1928). He wrote the history of the Library, privately printed at his expense in Norwood, Massachusetts, in 1918. He also assembled the old unpublished manuscript reports of the Library, had them typed and sets bound for the use of the officers of the Library. In 1918 Mrs. Farlow made a gift of the main passenger elevator, long needed since 1901.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41351

PRESENTATION OF CASE

A fifty-nine-year-old woman entered the hospital because of jaundice.

Seven months before admission after her husband died of a "heart attack," the patient became depressed, lost her appetite and began to lose weight. Two and a half months before admission Thorazine (chlorpromazine) was prescribed and was taken by mouth for approximately two weeks. The dosage was not known, but the patient had consumed about 60 pills. In the ensuing weeks dark urine, light stools and eventually jaundice developed. These signs were not accompanied by pain, discomfort, nausea, vomiting or increased anorexia. She was admitted to another hospital, where a diagnosis of hepatitis was made, and she was sent home on a high-protein, high-carbohydrate diet. Weight loss continued (25 pounds in the eight months before admission); jaundice fluctuated in intensity, but never completely cleared; the urine became lighter, and the stools darker. Marked pruritus accompanied the jaundice.

Three years previously the patient had had an attack of midline abdominal pain, which began at night, radiated to the back and one shoulder and was relieved by medication. Radiologic studies revealed a normal gall bladder; no stones were seen. One year before admission a second attack of pain had its onset in the morning, but was relieved by rest. The pain was midline and substernal and was "not quite the same" as the previous episode, but it was attributed by the patient to the gall bladder. Medical attention was not sought on this occasion. She had been treated with "iodine" for thyrotoxicosis in the past, but had not received any treatment for several years. Her father had had diabetes. She denied the use of alcohol or exposure to toxic chemicals. There was no known exposure to others with jaundice or liver disease.

Physical examination revealed a well developed, poorly nourished woman in no distress. Jaundice was marked, and there was evidence of recent weight loss. Multiple healing excoriations were noted over the legs, arms and back. The scleras were also icteric. A Grade 3 systolic murmur was loudest in the fourth left intercostal space, but was heard along the entire left sternal border. The upper edge of the liver was percussed at the sixth intercostal space, and the inferior edge was felt 3 cm. below the right costal margin in the midclavicular line. The liver edge was sharp, smooth and soft.

The temperature was 98°F., the pulse 92, and the respirations 20. The blood pressure was 140 systolic, 80 diastolic.

On urinalysis, there was a +++ bile test; 2 red cells and 10 white cells per high-power field, with frequent small clumps of white cells, were present in the sediment. Examination of the blood revealed a white-cell count of 7100, with a normal differential, and a hemoglobin of 13.4 gm. per 100 cc. On smear, a slight macrocytosis was noted, but the platelets were normal. The total serum bilirubin was 22.4 mg., the alkaline phosphatase 9.5 units, and the serum amylase 5 Russell units per 100 cc. The prothrombin time was 12 seconds (normal, 13 seconds); cephalin flocculation was negative at twenty-four and forty-eight hours; thymol flocculation was negative, and thymol turbidity was 2.8 units per 100 cc. The blood Hinton test was negative. The guaiac test on gray stool specimens was negative. The urinary urobilinogen was 1.31 Ehrlich units. An upper gastrointestinal series was normal.

On the fourth hospital day, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. RITA M. KELLEY*: This problem resolves itself into the etiology of jaundice in a middle-aged woman. The history of the way in which this disease appeared, the pruritus, the physical findings of excoriations and the slightly enlarged, presumably nontender liver and above all the laboratory data point unequivocally to an obstructive as opposed to a parenchymatous type of jaundice. I do not believe the details about the remote past history have any relation to the present illness. In any patient, of course, with a history of thyrotoxicosis, particularly one in whom the treatment was in no way curative, — unless this iodine was radioactive, and I do not believe it was, — one is always suspicious of recurrence of thyrotoxicosis, particularly after emotional trauma. The weight loss, depression and loss of appetite could be explained on the basis of resurgent thyrotoxicosis, unrelated to the jaundice. Jaundice does appear occasionally in rampant thyrotoxicosis, but I think it would be extremely unusual in this situation. Because of the absence of any further pertinent historical details and the complete disregard of the thyroid gland, or ramifications thereof, on the physical examination, I think that the

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person who abstracted the history is leading me away from thyrotoxicosis and that this had no relation at all to the present situation.

I should like to confine my discussion to the causes of obstructive jaundice. There are three diagnoses to consider: common-duct stone; cancer, either primary in the pancreas, the biliary tree, or the ampulla of Vater or possibly secondary, with pressure against the ducts causing obstruction; and intrahepatic biliary thrombotic disease secondary to the administration of chlorpromazine. I am ignoring rare causes of obstructive jaundice such as strictures and parasitic infestations of the biliary tree. I have no reason to suspect parasitic infestations certainly, and I believe that a diagnosis of benign stricture of the biliary tree can be made only at operation.

Three years before admission this patient had an attack that was most suggestive of biliary disease in its onset, its localization and so forth. This attack could certainly have represented the passage of a stone into the common duct or possibly just a transient inflammatory process in the gall bladder. The normal cholecystogram shortly after that attack militates against a gall bladder full of stones although we know that a normal cholecystogram can be obtained in the presence of several very small stones. Possibly, the patient had a solitary stone, which was passed at the time of the pain. The second attack of pain was not characteristic of gall-bladder pain; however, it is well recognized that gall-bladder disease can simulate angina. I assume that this attack was not well documented, and I cannot believe that it represented gall-bladder disease in the absence of further history. The majority of patients with common-duct stones give a past history of symptoms referable to the gall bladder. Many have had so-called indigestion or dyspepsia for years; often they have had right-upper-quadrant discomfort, and many have had one or more attacks of frank biliary colic with or without transient jaundice. Pain is a predominant feature of common-duct stone in about 80 per cent of cases; the patient under discussion did not have pain with the recent attack. However, we are all well aware of so-called silent stones, which with ball-valve action can cause fluctuating icterus with changes in the color of the stools and urine. On the basis of the history I cannot rule out definitely a stone in the common duct as the cause of the patient's present picture.

A malignant process must be strongly considered in a woman of fifty-nine years, particularly with a history of weight loss. At present the old dictum that painless jaundice differentiates carcinoma primarily of the head of the pancreas or of the gall bladder or biliary tree from a stone in the common duct is no longer accepted; it is now believed that nearly all patients with a stone and also nearly all with blockage caused by tumor eventually have pain. If this was a malignant process, the chances statistically are that it was not a carcinoma of the head of the pancreas, which is very rare in females, but was much more probably a primary carcinoma of the gall bladder or of the biliary tree. Carcinoma of the gall bladder is almost always seen in association with stones; again, to make this diagnosis, I should like to have a history of evidence of gall-bladder disease in the past. Also, with a malignant lesion, icterus is usually steadily progressive rather than fluctuating. These tumors do not slough and therefore are not accompanied by a transient lessening of the icterus. When icterus has been present for more than a few weeks I should expect the stools to be totally acholic; yet I am told that the stools were becoming darker rather than lighter — another point against the totally obstructing type of carcinoma. In carcinoma of the head of the pancreas one would expect an even greater weight loss and more progressive cachexia than this patient demonstrated. Such patients often lose 25 pounds in a few weeks. I assume that this patient had a slow steady loss over an eight-month period.

A carcinoma of the ampulla of Vater could explain the symptoms. That lesion often presents as primary painless jaundice, which is often fluctuating, because this tumor tends to slough into the opening of the duodenum, with temporary relief of the obstruction accompanied by lessening of the icterus, darkening of the stools and lightening of the urine. However, a patient with enough sloughing of the tumor to result in lessening of jaundice, is usually anemic because of the blood loss associated with the sloughing and often has intermittently guaiac-positive stools. Therefore, although the patient's anorexia, weight loss and age favor a malignant process, I do not believe that she had a primary malignant tumor in the pancreas, gall bladder, biliary tree or ampulla of Vater. I have no reason from the available data to suspect that she had a secondary tumor, with metastases in lymph nodes pressing on the common duct. Nor is there any reason to suspect that she had a lymphomatous process.

The third diagnosis worthy of consideration is the iatrogenic disorder engendered by administration of chlorpromazine, which has enjoyed worldwide popularity because of antiemetic properties and tranquillizing effects. In the past few months there have been several small series of cases of jaundice among the many large series of patients treated with chlorpromazine. For some strange reason this complication has been more evident in the short time since the drug came into wide use in the United States than it was in the past several years during which the drug had been used in Europe. Icterus characteristically appears after two or three weeks of therapy with varying dosage. It may be preceded by mild grippe-like symptoms and a slight fever; it may be accompanied by marked pruritus or may be totally asymptomatic except for icterus. Laboratory studies reveal a classically obstructive type of jaundice, with an increase in the bilirubin, seldom exceeding 15 or 20

mg. per 100 cc., however; an elevated alkaline phosphatase; bile in the urine; and light stools. The tests of parenchymal hepatic function are invariably normal; there is no evidence of permanent damage to the liver. A few of these patients have had a transient eosinophilia, which the patient under discussion did not have. At exploration the extrahepatic biliary passages have been found to be perfectly normal, and the biopsy of the liver has revealed a picture identical with that seen in patients who have become icteric while taking methyl testosterone. There is simply a blockage of small biliary radicles with bile thrombi and bile stasis, surrounded by varying degrees of inflammatory reaction. In most of these cases the icterus has subsided within three weeks of the cessation of Thorazine therapy; however, in a few patients, it has persisted for as long as five months. Although the patient under discussion was somewhat more icteric than most of these patients have been and the fluctuating nature of the jaundice is disturbing, I believe that she was suffering from the type of biliary blockage caused by chlorpromazine. I base the diagnosis on the time of the appearance of the icterus and the fact that the symptoms did not increase markedly at the time that she became jaundiced. The weight loss and anorexia can be adequately explained on the basis of a reactive depression, which began after the death of her husband; I do not believe I need to take them into consideration in the explanation of the icteric process. I have no feeling of security in this diagnosis, and if this were my patient I should certainly invite operation to be sure that with jaundice of such long duration she did not have a stone in the common duct.

I have not looked at the x-ray films. In this situation negative information will be of no help; positive information might be of some assistance.

DR. C. C. WANG: I am afraid I cannot help you. The gastrointestinal series is perfectly normal: there is no evidence of varices in the esophagus; the stomach and duodenal cap are normal; the duodenal loop is not widened; and there is nothing to suggest a space-occupying lesion in the head of the pancreas.

DR. KELLEY: Is there anything in the area of the gall bladder that could be stones?

DR. WANG: There are no calculi that I can see.

DR. JACOB LERMAN: Do you know exactly when the jaundice and signs of liver disease developed in relation to the consumption of the pills? It is not clear in the protocol.

DR. DANIEL S. ELLIS: As near as I remember the jaundice developed after the patient had been taking chlorpromazine for two or three weeks. The pills were stopped immediately.

DR. LERMAN: There is an article in a recent issue of the *Lancet*[1] describing 800 patients treated with chlorpromazine. The authors found that about 8 per cent of the patients manifested toxic symptoms and 1.5 per cent jaundice. They make the statement that the jaundice developed only while the patients were taking the drug and not after they had stopped taking it.

DR. ELLIS: In some cases jaundice has developed a week after the drug was stopped.

DR. LERMAN: I too have seen such a patient.

DR. MOSES M. SUZMAN (Johannesburg): I have seen a patient in whom jaundice developed after chlorpromazine was discontinued, but it disappeared after a while.

DR. FARAHE MALOOF: You are sure that this patient stopped taking the drug?

DR. ELLIS: Yes; she did stop taking it.

DR. MALOOF: Jaundice might appear a day or so after the drug was stopped; there might be a delayed reaction, as with penicillin. It is difficult to believe that it would develop that long afterward.

DR. BERNARD M. JACOBSON: Is it not possible that the patient already had an elevated bilirubin before she noted jaundice?

DR. BENJAMIN CASTLEMAN: That is the reason why patients who receive chlorpromazine should have tests for bile in the urine while they are being treated.

DR. JACOBSON: I happened by accident to do a bilirubin determination on a patient of mine who was taking chlorpromazine. It was high, so that we stopped the drug. The patient did not look jaundiced, and did not complain of any symptoms, until three days later.

DR. MALOOF: What is the shortest time in which the jaundice has developed after treatment?

DR. ELLIS: It has been reported to appear within two days to three weeks of the first administration of the drug. There must be considerable doubt about the etiology of the jaundice when it appears quickly in two days. On the other hand there are enough cases now in which other causes of jaundice have been eliminated to make one believe that the jaundice may occasionally develop within twenty-four to forty-eight hours after the start of drug therapy.

DR. SUZMAN: May I ask whether the blood lipids were determined? I ask this because in the case I saw recently the blood lipids, including the cholesterol, were extremely high.

DR. CASTLEMAN: Does that not occur in any case of long-standing obstructive jaundice?

DR. SUZMAN: Yes; but this was short-term jaundice. I have seen it in a patient whose jaundice was less than two months.

DR. JACOBSON: There is no report of the cholesterol level in the record.

CLINICAL DIAGNOSIS

Jaundice from chlorpromazine.

DR. RITA M. KELLEY'S DIAGNOSIS

Intrahepatic biliary blockage as result of chlorpromazine therapy.

Anatomical Diagnosis

Bile stasis, as result of chlorpromazine therapy.

Pathological Discussion

Dr. Castleman: This patient was seen by Dr. Ellis, who wrote as follows before the operation:

> I think the patient has an obstructive type of jaundice and not a viral hepatitis. Whether it is the type of jaundice caused by chlorpromazine or that resulting from extrahepatic biliary obstruction, such as a stone or neoplasm, I cannot tell, and I find no clues in the record to help me. In view of the fact that she has been ill for two months, I think that she should be explored, a cholangiogram done, and the common duct drained if no obstruction is found. I believe that there is no urgency about operating on her. It would be wise to prepare her for a week and then go ahead if no contraindication appears by that time.

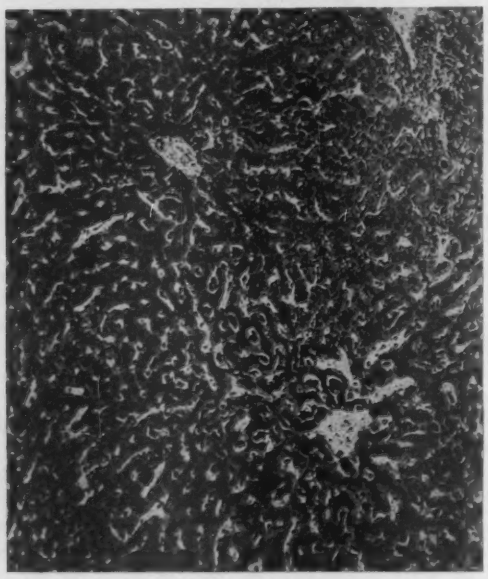

Figure 1.

He ended by saying, "This patient has a small liver. The edge is sharp, smooth and soft. I shall bet on chlorpromazine as the cause of the jaundice as opposed to stone or tumor."

Have you anything more to add, Dr. Ellis?

Dr. Ellis: No; that sums up my opinion about her before operation. I believed that there was no urgency in operating on her, for we might have found that the jaundice had subsided if we had waited. On the other hand she had been jaundiced for over two months without any significant improvement, and there was no real reason to believe that there would be improvement. Therefore it seemed wise to plan surgical exploration.

Dr. Castleman: She was operated on by Dr. Claude E. Welch; at operation he found no evidence of any extrahepatic obstruction. All the ducts and the gall bladder were normal; there were no stones. He believed that the jaundice probably was due to chlorpromazine and took a biopsy of the liver. Microscopically, the liver showed dark-brown areas of canaliculi plugged with the bile thrombi. These thrombi were especially numerous around the central veins, which are the areas affected in obstructive jaundice (Fig. 1). There was no cellular reaction around these areas of bile thrombi. The only clue that we as pathologists have that the findings may not be the result of extrahepatic obstruction, when we see an aspirated needle biopsy and are told nothing about the patient, is the lack of inflammatory reaction, which is usually seen if the stasis is due to a stone or a tumor obstructing the common duct. In some of the cases of chlorpromazine jaundice that has been present for a long time — there are patients who have been jaundiced seven or eight months — we do see some cellular reaction. During the last three months we have had 3 cases of chlorpromazine jaundice; those biopsies showed a similar picture.

Dr. Ellis was at the recent Atlantic City medical meetings at which several papers on this condition were read. Would you tell us about it, Dr. Ellis?

Dr. Ellis: Two papers were presented at the meetings in Atlantic City. Gambescia et al.[2] gave a clinical report of 5 cases of this type of jaundice, manifested by abrupt onset of malaise and fever. The laboratory data were important in that most of the patients had eosinophilia, hypercholesterolemia, increased serum bilirubin and increased alkaline phosphatase, with a normal flocculation test, normal albumin-globulin ratio and normal protein. The physicians believed that, because of the abrupt onset with malaise and the high eosinophilia, this was probably a hypersensitivity reaction. The other paper was by Menging, Grindlay and Cain,[3] of the Mayo Clinic, who have done some interesting experimental work in dogs. They cannulated the common bile ducts in dogs and recorded the ductal pressures for several weeks to determine the normal pressures. Then, after they had administered large doses of chlorpromazine, they believed that they could demonstrate definitely increased intraductile pressures and decreased motility in the duodenum. They wondered whether or not the increased spasm of the sphincter of Oddi and the decreased duodenal motility might lead to increased intraductile pressure and thereby to jaundice. I do not think that that is substantiated clinically because in the patients who have been operated on — this woman and 2 other patients in this hospital — cholangiograms taken at the time of operation or soon thereafter showed no dilatation whatsoever in the biliary tree; if anything it was smaller than normal. In addition the gall bladders were almost without bile and, in 2 cases, were wrinkled and shriveled, without bile. It is difficult for me to understand why, if there was increased intraductile pressure, the bile duct was not dilated and the gall bladder did not contain a great deal of bile.

About the point that Dr. Jacobson raised — that liver damage may be asymptomatic in patients who have been taking chlorpromazine — someone in the discussion reported 278 cases in which that drug had been administered. Five per cent of the patients had abnormal liver-function tests without clinical jaundice; in 1 per cent jaundice developed.

I have talked with several people who have a great deal of information about this problem. It seems that about 1 per cent of the patients receiving chlorpromazine have had clinical jaundice. The drug is not always innocuous, but in most of the patients the jaundice does disappear. The patient under discussion, whom we believe to have had jaundice from this source, after three months is still jaundiced and significantly incapacitated. Even more serious outcomes have been reported. I think chlorpromazine carries a real hazard, and one that we have to take into consideration every time we prescribe the drug. It certainly should not be prescribed for simple nausea.

A PHYSICIAN: I have heard that jaundice is less likely to occur if the drug is injected rather than taken by mouth. Have you any comment on that?

DR. ELLIS: I am told by the people who make the drug that that is true.

A PHYSICIAN: I should like to ask if there is any evidence about what happens to the biliary tree once the jaundice has disappeared. Does that become normal again?

DR. CASTLEMAN: Yes; the liver reverts to normal. Biopsies have been taken during the phase of chlorpromazine jaundice and again after the jaundice has disappeared.[4]

DR. ELLIS: That brings up another point — namely, how can one tell beforehand whether one is dealing with this type of jaundice or with obstruction? Physicians at the meetings said that they could differentiate this type of jaundice histologically, the characteristic findings being edema around the cholangioles in the portal spaces and eosinophil infiltration in the liver. However, when I pinned those physicians down after the meeting, they admitted that in 50 per cent of the cases they could not tell. If one cannot tell in 50 per cent of the cases, the differentiation is not very satisfactory.

DR. CASTLEMAN: A biopsy showing bile stasis without any evidence of an inflammatory reaction would make me lean toward a diagnosis of chlorpromazine jaundice rather than extrahepatic obstruction; obviously, this is not foolproof.

DR. ELLIS: Certainly, in any acute case in which jaundice was present from one to three weeks, I believe a needle biopsy should be done before an exploration. In a patient such as this, in whom jaundice had been present over two months, I think an exploration is the only way to establish the diagnosis.

DR. SUZMAN: Have you any evidence that the bile-thrombi formation was due to changes in the composition of the bile?

DR. CASTLEMAN: I cannot answer that.

DR. SUZMAN: It might be an effect directly on the bile formation.

DR. CASTLEMAN: You mean that the drug may affect the bile itself and make it more viscid — analogous to the mucoviscidosis associated with pancreatic fibrosis.

DR. ELLIS: That is one of the theories. Many other theories have been proposed. They are being tested experimentally.

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CASE 41352

PRESENTATION OF CASE

A fifty-three-year-old man was admitted to the hospital because of severe abdominal pain.

Five days before admission, when fever and a sore throat developed, he was ordered to bed by his physician. He had no cough or pain in the chest. Three days later vague epigastric distress and gaseous eructations began. On the morning of admission, four hours before admission, he was suddenly seized by epigastric pain, which became generalized within a short time. He was nauseated and vomited recently ingested food. The pain did not radiate to the back or shoulder. He had had no melena, hematemesis, constipation or diarrhea.

A peptic ulcer (?duodenal or gastric) had been demonstrated by a gastrointestinal x-ray series five years previously after symptoms of epigastric pain. He was treated by his physician with medications and a bland diet that he had since followed only as dictated by symptoms. He experienced periodic episodes of epigastric pain and "heartburn."

Physical examination revealed a flushed, toxic-appearing man in acute pain and very reluctant to change position. The heart was normal. The lungs were clear except for a few inspiratory sticky rales. The abdomen was tense and tender throughout. The tenderness was rated ++++ in the epigastrium and ++ in the right lower quadrant. Very rare peristaltic waves were heard. Rectal examination was negative.

The temperature was 102°F., the pulse 120, and the respirations 30. The blood pressure was 130 systolic, 80 diastolic.

The urine was normal except for granular and

hyaline casts and a few red and white cells per high-power field in the sediment. Examination of the blood revealed a hemoglobin of 17 gm. per 100 cc. and a white-cell count of 7400. The sodium was 136 milliequiv., the potassium 3.5 milliequiv., and the chloride 94 milliequiv. per liter; the nonprotein nitrogen was 47 mg., and the amylase 8 Russell units per 100 cc. A guaiac test on the stool from the rectal

FIGURE 1. *Roentgenogram of the Chest, Showing a Small Amount of Air beneath Each Leaf of the Diaphragm (Arrows).*

examination was negative. A plain film of the abdomen showed gas-filled loops of small and large bowel and free air under both leaves of the diaphragm. An x-ray film of the chest showed linear atelectasis in both bases (Fig. 1). An exploratory laparotomy was done three hours after admission, and a perforated gangrenous appendix with abscess formation was found. An appendectomy and drainage were performed.

The patient did fairly well postoperatively. His temperature remained practically stable between 98 and 100.5°F. On the ninth postoperative day he had a chill followed by a temperature of 102°F. On the eleventh postoperative day he complained of sudden weakness, and melena developed. The hemoglobin dropped from 13.1 gm. per 100 cc. postoperatively to 8.5 gm.; the white-cell count two days after operation was 15,200, rising to 36,000 a week later, and the hematocrit fell from 48.5 to 30 per cent. He was given three transfusions on the eleventh postoperative day and seven the next day. He continued to have loose, black stools estimated to amount to 2100 cc. On the thirteenth postoperative day he slipped into borderline collapse and vomited a small amount of blood. The blood pressure had a tendency to fall, and the pulse to rise. After three more transfusions had been given a subtotal gastrectomy and an anterior Hofmeister antiperistaltic anastomosis with double jejunostomy were performed on the thirteenth day after appendectomy. At operation a greatly dilated, blood-filled stomach was found. A preliminary gastrotomy was done to evacuate the clots, and shallow ulcerations were seen along the lesser curvature. In addition to the gastrectomy, two ulcers of the duodenum were excised. Pathologically, the gastric and duodenal lesions showed active peptic ulceration. Thirteen transfusions were given during and immediately after the operation. Postoperatively, the gastric tubes drained more blood clots, and he continued to have bloody stools totalling approximately 4000 cc. on the second postgastrectomy day. He continued to receive transfusions. Peristalsis was scant. He complained of extreme abdominal pain on the fourth postgastrectomy day, which was relieved after the jejunostomy was unclamped and about 500 cc. of red and chocolate fluid drained. Abdominal distention precipitated separation of the edges of the wound on the tenth postgastrectomy day, and about 500 cc. of purulent, foul-smelling small-bowel contents was drained from the wound. The abdomen was quiet.

The electrolyte losses sustained from jejunal catheter drainage were replaced by parenteral injections of fluids. The course was one of a gradual decline, but he remained conscious and alert and was never in severe pain. The persistent postoperative gastrointestinal blood loss through the tubes and rectum was treated with 26 blood transfusions. The hemoglobin varied from 6.5 gm. to 13.5 gm. per 100 cc. during the postgastrectomy course. The prothrombin, clotting and clot retraction times were normal. The blood fibrinogen level was 0.34 gm. per 100 cc. A tourniquet test was negative. He died eleven days after the gastrectomy.

DIFFERENTIAL DIAGNOSIS

DR. S. PETER SARRIS*: The simplest explanation of massive bleeding in a man with a long-standing peptic ulcer (who also had a perforation of a gangrenous appendix, which is rather common) is that postoperatively the peptic ulcerations became reactivated. He may have been one of the unfortunate ones in whom serious complications set in after gastrectomy, particularly an emergency gastrectomy in a bled-out patient. All the symptoms and signs that he had we see from time to time as the result of complications of gastric surgery, as complications of the peptic-ulcer diathesis or as complications of errors in technic during operation. For instance, the duodenal stump may have blown out, with subsequent peritonitis that finally reached the wound level and produced the foul-smelling abscess. The

*Clinical associate in surgery, Massachusetts General Hospital; chief surgeon, Union Hospital, Lynn, Massachusetts.

suture line may have leaked and resulted in peritonitis, or a loop of bowel may have been caught inadvertently in the wound closure. I assume that the double jejunostomy was done through a stab wound, as it usually is, and that the jejunum was not brought out through the wound, so that a loop of bowel may have been caught. The jejunostomy tube may have produced an obstruction or volvulus, which is a complication that we occasionally see after a jejunostomy. He may have bled from an unsutured vessel in the Hofmeister turn-in or in the anastomosis. Bleeding can also occur after a posterior gastroenterostomy from a so-called retrograde intussusception of the afferent loop with gangrene, although that is a rare complication. He may have continued to bleed from superficial ulcerations remaining in the gastric stump that were not seen at operation. A major vessel such as the superior mesenteric artery may inadvertently have been completely or partly sutured. Unfortunately, we see all those complications from time to time; they are risks of gastric surgery, particularly emergency gastric surgery.

Why do I not say that this explained the entire picture? I have three reasons for probing further. In the first place I do not think that Dr. Castleman asked me to discuss this case to emphasize the pitfalls of gastric surgery or of bleeding peptic ulcer. Secondly, it is unusual for a patient to have so many complications of gastric surgery. Thirdly, and most important, there was free air under both leaves of the diaphragm. I daresay that since there was free air under both leaves of the diaphragm with the evidence of peritonitis, the surgeons first made an incision in the upper abdomen and explored for a perforated duodenal ulcer because in a patient with a known peptic ulcer that would be by far the more likely diagnosis. I shall ask later to be told whether that was so because it will mean a great deal when I decide what the patient had. My impression is that free air under the diaphragm, certainly in any substantial amount, is rare with a perforated appendix. To be sure, we do not do an x-ray study in the sitting position on every patient who has a ruptured appendix, but in the great number that I have seen, I have not seen free air under the diaphragm. I am not talking about the development of bilateral subdiaphragmatic abscesses, which were particularly common before antibiotics and with which there may be bubbles of air free under both leaves of the diaphragm, fluid levels and so forth. I am talking about the initial phase of the perforation. There are good reasons for that: an acutely inflamed appendix over 95 per cent of the time does not perforate at the junction of the cecum, where there is a fair amount of air, but distally, where there is very little air. Moreover, and more important, the inflammatory process around the appendix precedes the perforation, and usually fairly successfully walls off the perforation — at least sufficiently so that free air does not escape.

Could this man have had simultaneously a perforated ulcer and a perforated appendix? If so, when the operator found the perforated appendix, which was a perfectly adequate explanation for the symptoms, he did not look around for more disease. I myself have never seen simultaneous perforation of the two, but I have seen them within a few days of each other. I shall be able to settle that if the information is available. At any rate I have to determine on the one hand what events, if not all, may have been due to the two known diseases, the gangrenous appendix and the peptic ulceration or to the complications of the diseases and operations or both; and on the other hand what may have been due to another underlying disease.

May I see the x-ray films?

DR. JOSEPH HANELIN: We have only films made before the first operation, which show a small amount of air under each leaf of the diaphragm, slightly greater in amount on the right (Fig. 1). I certainly agree that it is rare to see free air under the diaphragm, from a ruptured appendix. Air may enter the abdomen in strange ways. Recently, we saw free air under the diaphragm after irrigation of a ruptured bladder.[1] One's first impression in the case under discussion is that of a perforated peptic ulcer. There is a large, dilated, fairly fixed loop of small bowel in the abdomen slightly to the right of the midline, which seems to maintain its position in the films taken both in the upright and in the supine position. This may be nothing more than localized paralytic ileus, but one wonders about fixation of a loop of bowel for some other reason. There is, in addition, gas in the region of the ascending colon and cecum, suggesting that these structures are displaced somewhat.

DR. SARRIS: Is there any evidence of gas in the intestinal wall itself?

DR. HANELIN: I cannot be sure of gas in the wall itself. The lungs look quite all right except for the atelectasis.

DR. SARRIS: Could I ask whether the upper abdomen was explored at the time of the appendectomy?

DR. AUSTIN L. VICKERY: The preoperative diagnosis was perforated peptic ulcer, and the upper abdomen was thoroughly explored.

DR. SARRIS: I shall go over the possible causes of postoperative bleeding. If this patient had peritonitis he was probably on Levin-tube drainage. We have occasionally seen massive hemorrhage, particularly along the lesser curvature, from ulcerations caused by long-standing intubation of a patient. That would not explain the future course. Did he have cortisone therapy? Sometimes, a patient does not get along too well postoperatively and is given cortisone for a boost. Of course, cortisone can precipitate bleeding in a patient with an ulcer diathesis. A possibility

that should be seriously entertained is a severe staphylococcal enterocolitis. As a rule that attacks the small and the large bowel, but there have been several cases in which the entire gastrointestinal tract from the esophagus down was involved. This man with a ruptured appendix probably had antibiotic therapy. Did he have that after the appendectomy?

DR. VICKERY: Yes; he was given Terramycin (chlortetracycline) intravenously for two days after operation and then Chloromycetin (chloramphenicol) by mouth was substituted.

DR. SARRIS: For how many days?

DR. VICKERY: He was on antibiotic therapy continuously.

DR. SARRIS: Unfortunately, we are seeing with increasing frequency severe gastrointestinal manifestations, many of them fatal, as a complication of antibiotic therapy. The antibiotic therapy knocks out the usual intestinal flora and permits a resistant staphylococcus to grow. Diarrhea, shock and high fever are the usual manifestations, but massive gastrointestinal hemorrhage has been seen. Was a stool culture or blood culture done on this patient?

DR. VICKERY: No.

DR. SARRIS: I cannot make that diagnosis without help from the Department of Bacteriology, but I have to consider it seriously.

This patient may have had an underlying blood dyscrasia — that is, a leukemia — that was not noticed in the blood smear. To be sure, he had a perforated appendix and bleeding from a peptic ulcer, but the underlying disease may have been the leukemia, with massive gastrointestinal bleeding and finally death. It may have been a peculiar disturbance in the blood-clotting mechanism. The prothrombin time and clotting time appear to have been normal, so that I cannot make that diagnosis. I am in no position to make a diagnosis of a rare bleeding tendency. I assume that all the transfusions were not of citrated blood. We know that a patient who is going to require many transfusions certainly should not receive only transfusions of citrated blood.

I have seen a bleeding Meckel diverticulum that was confused with an acute appendicitis by a competent surgeon. The Meckel diverticulum had perforated and produced a severe reaction around the appendix, with pus formation. The appendix was removed, and later the perforated Meckel diverticulum was found. That would not explain the blood in the stomach of the patient under discussion.

Peculiar multiple septic emboli from an underlying septicemia have to be considered, but again I cannot make that diagnosis without a blood culture. What about varices? I do not believe that the surgeon could have resected the stomach without noticing the presence of portal hypertension. Nor could he have missed congenital multiple telangiectases. Midbrain lesions can produce peptic ulcerations, but there was no evidence of such lesions.

The bleeding lesion may have been missed at operation. It may have been a bleeding duodenal ulcer that was turned in with the duodenal stump — two ulcerations were removed. A bleeding lesion such as a small carcinoma or leiomyoma may have been left in the fundus of the stomach. I was stumped in this amphitheater nine years ago by a case[2] of a cirsoid aneurysm of the stomach, which produced massive bleeding. Perhaps after nine years Dr. Castleman thought he had better give me a similar case. I am sorry, but I cannot make that diagnosis.

One other disease that demands serious consideration — I was hoping to get help from the radiologist — is pneumatosis cystoides intestinalis, a disease that I discussed here about a year ago.[3] Free air under the diaphragm that is asymptomatic and peptic ulceration are two findings that are almost pathognomonic according to some experts. In the case under discussion there was free air under the diaphragm and long-standing peptic ulceration, but there was also a ruptured appendix. Then, can I explain the free air under the diaphragm on the basis of a ruptured appendix alone? Air under the diaphragm with a perforated appendix is sufficiently infrequent to warrant the consideration of such a rare disease as pneumatosis cystoides intestinalis. This can explain the entire picture, for a perforated appendix may be a complication of it. Massive gastrointestinal bleeding, although very common in children with pneumatosis, is unusual in adults, but several patients have had exsanguinating gastrointestinal bleeding. There is a sign, which I do not see here: the so-called floating sign; because of the air sacs around the small bowel, it floats up under the diaphragm. In this film, particularly in front of and above the liver, one should see large or small bowel if this were pneumatosis. The other sign that I looked for was the scalloping rings of air around the bowel. In the absence of positive evidence all I can do is mention that diagnosis. Also, this small amount of free air could have come from the ruptured appendix.

My first diagnosis will have to be on a statistical basis — that is, bleeding from an ulcerating lesion of the fundus of the stomach that was missed at the time of operation together with a train of postoperative complications. I should like to mention almost equally seriously pneumatosis cystoides intestinalis.

CLINICAL DIAGNOSIS

Perforated peptic ulcer.

DR. S. PETER SARRIS'S DIAGNOSIS

Bleeding peptic ulcer of stomach.
?Pneumatosis cystoides intestinalis.

Anatomical Diagnoses

Acute peptic ulcerations in stomach remnant, with massive bleeding.

Ruptured stump of appendix, with generalized peritonitis.

Operations, recent: appendectomy for acute perforated appendicitis; subtotal gastrectomy.

Partial intestinal obstruction, transverse colon, by afferent loop of jejunum of gastrojejunostomy.

Pathological Discussion

Dr. Vickery: When the abdomen was opened at autopsy there was a large amount of purulent, fecal-smelling exudate scattered over the serosal surfaces in addition to distinct pockets of pus. The gastrojejunostomy stoma was intact, and the jejunostomy stomas were likewise in good order. There was, in other words, no evidence of leak from the previous gastrectomy procedure — all the anastomoses and turns-in were intact. The stomach remnant was filled with clotted blood, and two large, superficial mucosal ulcerations were noted. One of these was located near the gastroesophageal junction and measured 3 cm. in diameter. There were numerous bleeding points in this ulcer base. The other ulceration was situated along the margin of the distal closed end of the stomach, and this measured 3.5 cm. in length. In addition the mucosa of the distal esophagus showed superficial ulcerations. These ulcerative lesions proved to be of the active, peptic type and undoubtedly were the source of the protracted gastrointestinal bleeding. No mucosal lesions or ulcerations were found in any portion of the small or large intestine. The gastric ulcerations found at post-mortem examination appeared to be of fairly recent duration whereas those removed at operation showed more fibrosis in their bases.

Now we have a cause for the bleeding. Do we have an explanation for the clinical sequence of events on which Dr. Sarris has theorized? Another finding of note in the abdomen was the blown-out stump of the appendix, which thus accounted for the generalized peritonitis, wound dehiscence and general wound sepsis. When did the rupture of the appendiceal stump take place? We cannot be certain of that. It seems that it took place a considerable time before death, probably antedating by at least several days the wound infection and dehiscence. Still another complicating factor was a partial obstruction of the proximal transverse colon, which was distended to 18 cm. in diameter. This was caused by extrinsic pressure of the afferent limb of the jejunum leading to the gastrojejunostomy, which passed anteriorly over the transverse colon. Exactly what role this might have played in the sequence of events is debatable. Whether it preceded, with its dilatation and pressure, the blowing out of the appendiceal stump is difficult to say.

I think the important point about this case, which has been touched upon by Dr. Sarris, is that it reveals some of the complications of gastric surgery. This man had a predilection for developing peptic ulcers, and the ulcerations that formed postoperatively and caused the massive bleeding are a known complication in such patients — a complication that is poorly understood.

Dr. Allen G. Brailey: Was there any evidence of enteritis?

Dr. Vickery: No; there was not. Nor did he have any other complications. He had more than his share.

Dr. Edward B. Benedict: Do you think that he had perforated the ulcer in the beginning?

Dr. Vickery: No; there was no evidence of perforation of any of the peptic ulcers.

Dr. Benedict: From where did the air under the diaphragm come?

Dr. Vickery: I assume from the appendix.

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Official Organ of
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REVERSAL OF TUBERCULIN REACTIVITY

IN 1953 Woodruff and co-workers[1] reported the results of observations on the course of tuberculin hypersensitivity in patients in whom chemotherapy for tuberculosis was begun when they were so seriously ill that they had a very low level of sensitivity to tuberculin. In every patient who responded favorably to the therapy, they found that hypersensitivity to tuberculin increased, and this occurred even before there was roentgenographic evidence of improvement. This finding may be considered as a clear demonstration of the remarkable effectiveness of modern chemotherapy in tuberculosis, a fact fully attested by the brilliant results currently being obtained, particularly in patients with miliary and meningeal tuberculosis.

The results of prolonged chemotherapy with the regimens now being employed have also raised the question whether true cures of tuberculosis may be achieved in some cases. This question was particularly pertinent with respect to patients with pulmonary tuberculosis who have had resections of residual pulmonary lesions after prolonged chemotherapy. The early reports of failures to demonstrate viable tubercle bacilli in the resected lesions of such patients gave some support to that possibility. Subsequent studies,[2] however, have indicated that, with proper technics, viable tubercle bacilli could be cultivated from the lesions from a majority of these cases so that the possibility of cures still remained to be proved.

One strong type of evidence for cure would be the demonstration of a reversal to negative of the tuberculin reaction of patients after therapy. In a previous editorial[3] it was suggested that observations on the tuberculin reaction of patients during the follow-up period after prolonged chemotherapy, particularly after resection of residual lesions, are urgently needed to help answer the important question of whether a true cure of tuberculosis is obtainable. Other situations in which the possibility of cure may be anticipated with the types of effective therapy now available are in the early exudative, noncavitary disease in adolescents or young adults and, even more so, in the early cases of primary tuberculosis in infants and children.

In a recent issue of the *Journal,* Robinson, Meyer and Middlebrook[4] reported the cases of 4 children under two years of age who had positive Mantoux reactions to old tuberculin and normal roentgenograms of the chest. They were all treated with isoniazid, 8 mg. per kg. of body weight per day. All of them became negative to old tuberculin in 1:100 dilution after six or seven months of treatment. Two other similar children, after five and six months of treatment, respectively, retained their hypersensitivity to a 1:1000 dilution of old tuberculin, as did 7 additional patients with originally positive reactions and positive roentgenograms of the chest.

Loss of skin hypersensitivity to tuberculin has been noted in laboratory animals during and after treatment with streptomycin or isoniazid, and some diminution in skin reactivity has also been noted in patients with tuberculosis who had been treated with such drugs, but the observations in human beings have been quite variable, and complete reversal has not been observed. The results reported by Robinson and his co-workers have indicated that a marked decrease or reversal of tuberculin hypersensitivity is more likely in primary tuberculosis with a minimum of involvement — that is, with negative roentgenograms. This is also taken as a justification for the treatment of such early, asymptomatic cases. It is further suggested that patients in whom treatment is so successful as to occasion complete loss of hypersensitivity and immunity might then be vaccinated with BCG in an attempt to prevent reinfection. If reinfection occurs, of course, they could again be given chemotherapy.

The authors did not offer the obvious suggestion that the treatment that was so successful in reversing the tuberculin test be continued indefinitely — perhaps at a lower dosage level. This is not recommended here but will undoubtedly be offered by others as a proper course to follow, and would be in line with the long-term regimens of prophylactic chemotherapy now being advocated for several other diseases by some workers. The feasibility, effectiveness and complications of such regimens are still to be explored.

Although the apparent reversal of the tuberculin reaction in 4 asymptomatic cases with negative roentgenograms may be considered as suggestive evidence of possible cures of tuberculous infections, the achievement of true cures in patients with demonstrable tuberculous lesions still remains to be accomplished. Moreover, it will be of considerable interest to observe patients in whom the tuberculin test is reversed and who subsequently get reinfected. Will these later infections be of the primary or of the reinfection type? It is hoped that, should such cases occur, they will be recognized early and carefully studied and reported by competent observers.

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AMA "SEAL OF ACCEPTANCE" ABANDONED

The American Medical Association, as announced and discussed in the issue of the *Journal of the American Medical Association* for July 30, 1955, has adopted new and more practicable programs for its various scientific councils. Under the new methods of procedure the evaluation of individual products in the line of drugs, foods, devices and cosmetics, as well as its seal of acceptance, have been abandoned in favor of judging the evidence regarding the more general values pertaining to groups or classes of products.

The revised attitude is a result both of the tremendous increase in the number and variety of pharmaceutical products that the Council on Pharmacy and Chemistry has been called upon to examine, and of the unwelcome commercial value that has been attached to Council acceptance and its seal. Therapeutic agents with a relatively narrow margin of safety or with a high index of serious side effects should not necessarily be condemned and discarded, according to the new program, but added responsibility is placed on physicians to know with what they are dealing and on manufacturers to state facts, good and bad, regarding their products, without equivocation. A case in point is supplied by the article and editorial on phenylbutazone published elsewhere in this issue of the *Journal*.

So far as the Council on Pharmacy and Chemistry is concerned, the meat of the matter is the termination of the seal-acceptance program with its implied endorsement of the product, in favor of a policy of supplying certain pertinent information about a new product or class of products. As stated by the Council, it now "does not accept, endorse, recommend, or guarantee any individual brand or preparation of a drug described in New and Nonofficial Remedies," nor does it test or analyze samples, review or investigate procedures in manufacture and control or enquire into the compliance of any firm with federal, state or municipal laws and regulations.

Its function will be rather "to evaluate available evidence relating to the actions, uses, dosage, hazards, and other pertinent properties of drugs and to encourage rational therapy by timely, informative reports to the medical profession." These reports will be in the form of monographs to the editor of the *Journal of the American Medical Association* for publication in the *Journal* and subsequent inclusion in *New and Nonofficial Remedies*. The Council will in general consider for such inclusion only drugs with a single active ingredient or extracts from a single source.

The principles on which advertising is accepted for the publications of the American Medical Association and presumably for the journals that subscribe to the State Journal Advertising Bureau of the Association have not changed, in principle. Approximately the same as those that the *New England Journal of Medicine* follows, the principles are based on ethical considerations:

1. The advertiser may be required to submit data in support of the usefulness of the product and the validity of the proffered claims.
2. Advertisements should not be deceptive or misleading.

3. Sweeping superlatives and unfair comparisons will not be allowed. Extravagantly worded copy is subject to revision or rejection.

4. Disparagement of a competitor's goods will not be allowed. Any claims for superiority must be supported by evidence acceptable to the Association.

5. Quotations or excerpts from a published paper are acceptable only if they do not distort the meaning intended by the author. Furthermore, the mere appearance of a paper, or of several papers, may not necessarily supply sufficient evidence to support the proffered product or claim, and the Association in such instances may request more complete data. When excerpts are taken from a published paper for use in an advertisement the Association may require the advertiser or his agent to obtain written permission for such use from the author and, if necessary, from the editor or publisher of the publication in which it appears.

6. If testimonials or quotations appear in advertising, the validity of the claims, the expert knowledge of the person offering the testimonial, and the probable effect of the advertisement on the reader will be considered. The Association may request evidence of the authenticity of the testimonial.

Other enumerated principles follow, but these six present the basic policies of the Association.

MATERNAL AND INFANT HEALTH

As noted in Dr. Silverman's letter published elsewhere in this issue of the *Journal*, the teaching program for mothers in the hospitals giving maternity services in Massachusetts has been practically nonexistent as such:

> This survey revealed that some hospitals had no teaching program whatsoever. Others gave no oral instructions but distributed outdated pamphlets advertising expensive and unnecessary products. The outstanding complaint from mothers was that they were given conflicting advice from hospital supervisors, public-health nurses, practical nurses and private doctors.

In an effort to correct this situation and produce a degree of uniformity, a committee of the Greater Boston United Community Services in conjunction with the Massachusetts Chapter of the American Academy of Pediatrics, under the chairmanship of Dr. Silverman, has prepared the outline mentioned in his communication. It has been published by the Massachusetts Department of Public Health and is in process of being distributed to the institutions that are, or should be, interested.

It is hoped that the brief message contained in this outline, so carefully prepared, will have the widest possible circulation. With all the valuable information available in the world today, it is a pity that so much misses its mark or has misinformation substituted for it.

POLIO MONEY RUNS SHORT

THE National Foundation for Infantile Paralysis on August 12 called upon its 3100 local chapters to surrender to the Foundation all their surplus funds in order that the nation's polio program might "survive." This unprecedented action resulted from the inadequacy, by $12,000,000, of last January's March of Dimes collection of $52,511,185.69 to meet the season's needs.

No accounting was given at this time of the expenditure of the Foundation's funds, or its effectiveness, although the implication is that much of it went for patient care. The contributions to the March of Dimes campaign have amounted to an average of about 30 cents from each person in the nation; they have been expended at the average rate of $500 for each victim of the disease.

We observe that Dr. West almost invariably orders for those of his patients at St. Bartholomew's, who are the subjects of fibrous tumors of the uterus, a long course of one or other of the preparations of iodine. The following is the prescription which was ordered for a middle-aged woman, who applied with that disease on Saturday: — Potassii iodidi, gr. j.; syrupi ferri iodidi, m. xx; aquae carui, oz. ss. Ter die sumend.

Boston M. & S. J., *Sept. 6, 1855*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

EDMUNDS — Fred A. Edmunds, M.D., of Woburn, died on July 17. He was in his seventy-eighth year.

Dr. Edmunds received his degree from Baltimore Medical College in 1903.

He is survived by a widow and two daughters.

MORIARTY — Patrick M. Moriarty, M.D., of Chicopee and Springfield, died on August 3. He was in his sixty-fifth year.

Dr. Moriarty received his degree from Georgetown University School of Medicine in 1913. He was a fellow of the American Medical Association and a member of the Chicopee Medical Society. He was formerly president of the physicians' staff, Mercy Hospital.

He is survived by his widow, one son and three daughters.

SCHILLANDER — Carl A. Schillander, M.D., of Springfield, died at Fort Lauderdale, Florida, on July 30. He was in his sixty-seventh year.

Dr. Schillander received his degree from Tufts University School of Medicine in 1910. He was a member of the Physicians Club of Springfield and a fellow of the American College of Surgeons and the Springfield Academy of Medicine.

He is survived by his widow, one son and a daughter.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

HURRICANE DAMAGE

The Massachusetts Department of Public Health advises all home owners, retailers and operators of cold-storage warehouses to take all possible precautions to anticipate possible power shortages due to hurricane damage, with resultant loss of refrigeration. Home refrigerators and freezers should be kept closed unless it is absolutely necessary to remove food for immediate use.

Dry ice can be used to maintain proper temperatures in refrigerators in case of power failure. Refrigerators and home freezers with seals made of rubber gaskets can safely be kept closed, even when dry ice is used, without risk of explosion from expanding gases.

Most home freezers will preserve their contents safely for at least twenty-four hours after power fails.

If further advice from the weather bureau places Massachusetts in the alert category, home freezers and refrigerators should be operated at maximum cold levels.

Even if food thaws out in a freezer, it can still be consumed with safety. However, caution should be exercised to make sure that food has not become decomposed. If this has happened, the food should be destroyed. Decomposition of meat and meat products can be detected by the odor.

Milk plants and other food-processing establishments handling perishable foods are advised to contact the Division of Food and Drugs, State Department of Public Health, for assistance in the event of power failure. Home owners, retailers, wholesalers and other handlers of perishable foods should notify local boards of health as soon as possible after their need for artificial refrigeration becomes apparent. The boards of health, in turn, should apply to the Food and Drugs Division for allotments of dry ice, which must be handled and distributed under local board-of-health supervision.

Steps have been taken to provide for additional supplies of dry ice to be brought into the State in case of an emergency.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date		Clinic Consultant
Greenfield	September	1	Charles L. Sturdevant, M.D.
Lowell	September	2	Albert H. Brewster, M.D.
Gardner	September	6	Carter R. Rowe, M.D.
Haverhill	September	7	William T. Green, M.D.
Brockton	September	8	George W. Van Gorder, M.D.
Salem	September	12	Paul W. Hugenberger, M.D.
Lynn*	September	12	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Worcester	September	16	John W. O'Meara, M.D.
Pittsfield	September	21	Edward J. Coughlin, Jr., M.D.
Hyannis	September	22	Paul L. Norton, M.D.
Fall River	September	26	David S. Grice, M.D.
Springfield	September	27	James D. Fisher, M.D.

Rheumatic-Fever Clinic	Dates
Fitchburg	September 7, 14, 21, 28
North Reading	September 13, 20, 27

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1955

RÉSUMÉ

Disease	July 1955	July 1954	Seven-Year Median
Chancroid	2	1	1
Chicken pox	531	380	439
Diphtheria	2	1	3
Dog bite	1330	1665	1450
Dysentery, bacillary	12	12	9
Encephalitis, infectious	1	4	3
German measles	86	116	121
Gonorrhea	189	165	186
Granuloma inguinale	0	0	0
Hepatitis, infectious	50	66	8*
Lymphogranuloma venereum	0	0	0
Malaria	0	4	4
Measles	501	2303	1162
Meningitis, meningococcal	10	3	4
Meningitis, Pfeiffer bacillus	1	1	2
Meningitis, pneumococcal	3	1	2
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	5	7	3
Mumps	348	953	614
Poliomyelitis	422	36	36
Salmonellosis	32	24	7
Scarlet fever	110	106	106
Syphilis	174	138	140
Trichinosis	2	1	2
Tuberculosis, pulmonary	254	141	221
Tuberculosis, other forms	11	9	14
Typhoid fever	0	0	3
Undulant fever	1	1	3
Whooping cough	70	161	130

*Six-year median.

Comment

Diseases below the seven-year median were diphtheria, German measles, measles, mumps, typhoid fever and whooping cough.

Only two cases of diphtheria were reported in July; this brings the total for the period beginning January 1 to only 16.

The 86 cases of German measles reported make this the lowest figure for this disease for the month of July since 1948.

Since no cases of typhoid fever were reported during July the total for the year so far is only 7.

The 70 cases of whooping cough reported represent the lowest figure by a considerable margin for this disease for the month of July in the history of the State.

Diseases above the seven-year median were chicken pox, bacillary dysentery, infectious hepatitis, poliomyelitis, salmonellosis and scarlet fever.

By a comfortable margin, poliomyelitis was at its highest peak for the month of July in the history of the State.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Anthrax: Walpole, 1; Wellesley, 1; total, 2.

Diphtheria: Barnstable, 1; Boston, 1; total, 2.

Dysentery, bacillary: Beverly, 3; Boston, 3; Danvers, 1; Hamilton, 1; Waltham, 3; Worcester, 1; total, 12.

Encephalitis, infectious: Pepperell, 1.

Hepatitis, infectious: Andover, 1; Boston, 2; Brockton, 1; Brookline, 2; Cambridge, 1; Chelsea Naval Hospital, 5; Cohasset, 1; Fall River, 3; Fitchburg, 1; Fort Devens, 1; Framingham, 2; Franklin, 1; Gloucester, 6; Haverhill, 1; Lowell, 2; Ludlow, 1; Lynn, 1; Milford, 1; Northampton, 1; Pittsfield, 1; Somerville, 7; Springfield, 3; Taunton, 1; Upton, 1; Wellesley, 1; West Bridgewater, 1; Worcester, 1; total, 50.

Meningitis, meningococcal: Boston, 5; Lynn, 1; Pittsfield, 3; Shirley, 1; total, 10.

Meningitis, Pfeiffer bacillus: North Andover, 1.

Meningitis, pneumococcal: Boston, 1; Dracut, 1; Worcester, 1; total, 3.

Meningitis, undetermined: Dedham, 1; Hanover, 1; Somerville, 2; Springfield, 1; total, 5.

Poliomyelitis: Arlington, 2; Barnstable, 1; Bedford A.F.B., 1; Bedford, 3; Belmont, 1; Beverly, 4; Boston, 182; Braintree, 9; Bridgewater, 1; Brockton, 10; Brookfield, 1; Brookline, 10; Cambridge, 7; Canton, 1; Chelsea, 6; Concord, 1; Danvers, 2; Dedham, 4; Dennis, 1; Dover, 1; Easton, 2; Everett, 1; Fall River, 5; Fitchburg, 2; Framingham, 3; Franklin, 1; Hampden, 1; Hanson, 1; Harwich, 1; Haverhill, 3; Holyoke, 1; Hudson, 2; Hull, 1; Kingston, 2; Lawrence, 1; Leicester, 1; Leominster, 2; Lexington, 4; Lynn, 4; Malden, 1; Marblehead, 1; Marlboro, 4; Marshfield, 2; Medford, 4; Middleboro, 3; Milford, 2; Natick, 3; Needham, 6; New Bedford, 1; Newton, 8; Northampton, 5; No. Reading, 1; Norwood, 3; Peabody, 3; Pembroke, 2; Plymouth, 5; Quincy, 7; Randolph, 4; Raynham, 1; Reading, 7; Revere, 6; Sandwich, 1; Scituate, 1; Sherborn, 1; Shrewsbury, 1; Somerville, 4; Springfield, 6; Sterling, 1; Swampscott, 1; Taunton, 5; Wakefield, 2; Walpole, 4; Waltham, 3; Wareham, 2; Watertown, 1; Wayland, 1; West Bridgewater, 1; West Springfield, 1; Westwood, 2; Weymouth, 16; Wilmington, 1; Worcester, 2; total, 422.

Salmonellosis: Agawam, 1; Belmont, 1; Boston, 7; Brookline, 3; Chelsea, 1; Danvers, 5; Fitchburg, 1; Hingham, 1; Hopkinton, 1; Newton, 2; Northampton, 4; Salem, 1; Somerville, 2; Springfield, 1; Swampscott, 1; total, 32.

Trichinosis: Medway, 1; Newbury, 1; total, 2.

Undulant fever: Weymouth, 1.

CORRESPONDENCE

c/o YOUR BABY

To the Editor: In an effort to improve services for mothers and infants, the Greater Boston United Community Services, in conjunction with the Massachusetts Chapter of the American Academy of Pediatrics, appointed a committee on maternal and infant health.

As one of its tasks the Committee checked some of the 126 hospitals giving maternity services in Massachusetts to determine what is being taught mothers regarding their own care and that of their newborn infants. This survey revealed that some hospitals had no teaching program whatsoever. Others gave no oral instructions but distributed outdated pamphlets advertising expensive and unnecessary products. The outstanding complaint from mothers was that they were given conflicting advice from hospital supervisors, public-health nurses, practical nurses and private doctors.

It became obvious that there was need for an outline that would facilitate teaching and co-ordinate the instruction programs of maternity hospitals, public-health nurses and so forth. With this in mind a leaflet, *Care of Your Baby,* was prepared to answer the mother's first questions about her new baby; it describes in some detail the technic of the bath, breast feeding, formula preparations and care of the mother herself.

It is hoped that the leaflets will be distributed on maternity wards to mothers the day after they have had their babies. The teaching nurse would then also use the leaflet as the basis for her oral instruction to the mothers.

The members of the working committee were Ellen J. Hendrickson, R.N., who deserves special credit; Dr. Samuel B. Kirkwood; Alice McKinnon, R.N.; Drs. Dane Prugh, William Schmidt and Irving Silverman, chairman; Alfred Weller, Misses Margaret Tracy, Mary E. Welsh, Verene Edmunds, Josephine Scelsi, Rosemary MacIsaacs, Eleanor Voorhies and Leona Vaughn.

Some of the persons who deserve credit for their suggestions and support in the preparation of this leaflet are: Drs. James M. Baty, Allan M. Butler, John H. Cauley, Stewart H. Clifford, Ralph W. Daffinee, Cannon R. Eley, John C. Faherty, Eli Friedman, Joseph Garland, Sidney S. Gellis, Merritt B. Low, R. Gerald Rice, Clement A. Smith, Richard M. Smith, Lendon Snedeker and John J. Treanor.

Through the interest and efforts of Dr. R. Gerald Rice, director of the Division of Maternal and Child Health, and Miss Ellen J. Hendrickson, maternity nursing consultant, the Massachusetts Department of Public Health will print these leaflets and distribute them free of charge. Any hospital in the State may obtain supplies of the leaflets by application to Public Health Nursing Section, Room 315, Ford Building, 15 Ashburton Place, Boston, Massachusetts.

IRVING SILVERMAN, M.D.
Chairman, Committee on Maternal and Infant Health, United Community Services
Brookline, Massachusetts

A CORRECTION

To the Editor: I wonder whether the figure, 8,000,000, mentioned in the editorial "E Pluribus Unum" that appeared in the May 5 issue of the *Journal,* is correct? I think there is one extra zero. We could not possibly have 8,000,000 deaths from heart disease each year in this country — maybe this should be 800,000. This figure was mentioned in the eighth line of the second paragraph of the editorial.

SAMUEL A. LEVINE, M.D.
Boston

Note: Dr. Levine correctly assesses the tremendous mortality that a misplaced zero can mistakenly imply. The correct number is mercifully 800,000.

ED.

BOOK REVIEWS

Sentence Completion: A projective method for the study of personality. By James Q. Holsopple and Florence R. Miale. 8°, cloth, 177 pp. Springfield, Illinois: Charles C Thomas, 1954. $5.50. (Publication No. 230, *American Lecture Series.)*

When Jung, about the turn of the century, discovered work-association tests, he opened a roadway that has been continued for many years by other workers. Most eminent perhaps among his followers was Herman Rorschach, Swiss psychiatrist, who died about 1922 after leaving the world his legacy of the ink-blot tests now so widely used, with various modifications. Almost as valuable is the new device of giving a subject an incomplete sentence and allowing him to complete it after his own fancy. This psychologic testing device has proved so useful that James Quinter Holsopple, of the Division of Clinical Psychology at the Veterans Administration, Washington, D.C., and Florence R. Miale, of the New School for Social Research, New York City, have prepared this stimulating monograph in which they outline the use of incomplete sentences as a valuable form of projective technic and show how sentence openings were developed. The characteristic completions are outlined in one section with full interpretation in 1 case (Abner). Thirteen illustrative records are remarkable for the insight shown and conclusions drawn in as many persons ranging from the findings in "Jeremy" (an executive) to "Ophelia," a patient who followed the example set by her namesake in *Hamlet.* An appendix gives the Miale–Holsopple sentence-completion blank, and the book as a whole gives a most complete and satisfactory picture of this valuable psychologic testing technic.

Of local interest is the foreword by Dr. Frederick L. Wells, dean of New England psychometrists and teacher of several

generations of medical students at Harvard Medical School. Dr. Wells is the only man living in Boston who was photographed with Freud when Freud visited Clark University in 1909. From that date to this he has had his eyes and mind open for diagnostic aids in dynamic psychotherapy. This book he introduces is a worthwhile exposition of one of the newest and most valuable technics.

MERRILL MOORE, M.D.

Operative Cholangiographie. By Priv.-Doz. Dr. Walter Hess. With a foreword by Prof. Dr. R. Nissen. 4°, cloth, 201 pp., with 150 illustrations and 14 tables. Stuttgart: Georg Thieme, 1955. DM 42.- $10.00. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

This volume is timely since the debatable question of operative cholangiography is now being discussed by all abdominal surgeons. It is the reviewer's opinion that this is the first treatise on the subject since Mirizzi's book, published in 1941.

Dr. Hess has brought out all the indications for and the pitfalls and results of cholangiography on the operating table. Excellent charts and graphs reveal the effects of disease and drugs on the pressures within the biliary system.

The section on chronic pancreatitis is particularly valuable, and will guide the surgeon in his diagnostic procedures for this poorly understood malady.

Illustrations are profuse, and by means of line drawings accompanying the photographed roentgenograms, the reader is made immediately aware of proper interpretation. One does not need to be a linguistic scholar to obtain a clear idea of the procedures.

The bibliography is extraordinarily complete, and this alone makes such a monograph valuable. Certainly, all surgeons practicing these technics will obtain points of information that will help them carry out these maneuvers. Those who are still skeptical about the value of cholangiography may well find valuable information in this book.

ARTHUR W. ALLEN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

1954 Medical Progress: A review of medical advances during 1953. Edited by Morris Fishbein, M.D. 8°, cloth, 345 pp. New York: Blakiston Company, 1954. $4.00.

There are 20 articles in this progress report written by 28 specialists in their particular fields. The literature is surveyed, and extensive bibliographies are appended to the articles. There is a good index. Although covering only one year this type of book should be in the reference collections of medical libraries.

Blood Groups in Man. By R. R. Race, Ph.D. (Cambridge), M.R.C.S. (England), Lister Institute, London; and Ruth Sanger, Ph.D. (London), B.Sc. (Sidney), Medical Research Council Blood Group Research Unit, Lister Institute, London. With a foreword by Professor Sir Ronald Fisher, F.R.S. Second edition. 8°, cloth, 399 pp., with 114 tables. Springfield, Illinois: Charles C Thomas, 1954. $7.50.

This new edition of a special book first printed in 1950 has been revised and brought up to date. A group has been added to the previous eight known groups, — the Kidd group, — and new chapters have been incorporated on this group and on linkage. Extensive lists of references are added to the chapters, and there are indexes of names and subjects. The printing was done in Great Britain; the publishing is excellent. This authoritative book is recommended for all medical libraries and all persons interested in the subject.

The Year Book of Radiology: Radiologic diagnosis. Edited by John Floyd Holt, M.D., professor of radiology, University of Michigan Medical School; and Fred Jenner Hodges, M.D., professor of radiology and chairman, Department of Radiology, University of Michigan Medical School. *Radiation therapy.* Edited by Harold W. Jacox, M.D., professor of radiology, Columbia University College of Physicians and Surgeons, and chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Morton M. Kligerman, M.D., associate professor of radiology, Columbia University College of Physicians and Surgeons, and assistant radiologist, Presbyterian Hospital, New York City. 8°, cloth, 432 pp., with 347 illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $9.00. (1954-1955 *Year Book Series.)*

The material abstracted in this volume covers the period June, 1953, to June, 1954, and is divided into two sections on diagnosis and radiation therapy.

Peripheral Vascular Diseases. By Edgar V. Allen, M.A., M.D., M.S. in medicine, Section of Medicine, Mayo Clinic, and professor of medicine, Mayo Foundation, Graduate School, University of Minnesota; Nelson W. Barker, M.D., M.S. in medicine, Section of Medicine, Mayo Clinic, and professor of medicine, Mayo Foundation, Graduate School, University of Minnesota; and Edgar A. Hines, Jr., M.A., M.D., M.S. in medicine, Section of Medicine, Mayo Clinic, and professor of medicine, Mayo Foundation, Graduate School, University of Minnesota; with associates in the Mayo Clinic and Mayo Foundation. Second edition. 8°, cloth, 825 pp., with 316 illustrations, 7 in color. Philadelphia: W. B. Saunders Company, 1955. $13.00.

This second edition of a standard book has been revised and brought up to date. New material includes aortography, coarctation of the aorta, purpura, hypertensive ischemic ulcers of the leg, technics of sympathectomy, nonvascular operation for intermittent claudication, surgical treatment of varices, aortic aneurysm and vascular injuries. The text is the joint work of 13 specialists and is based largely on their experience at the Mayo Clinic. Lists of references are appended to the chapters; there is a good index, and the publishing is excellent. The book is recommended for all medical libraries and all interested physicians.

Clinical Orthopaedics. Edited by Anthony F. DePalma, with the assistance of associate editors and a board of advisory editors. Number 4. 4°, cloth, 240 pp., with illustrations. Philadelphia: J. B. Lippincott Company, 1954. Single numbers $7.50; sustaining, $5.00.

The text of this new volume of a standard series is divided into two parts, on joint fractures and dislocations and general orthopedics. There are 22 articles, and short lists of references are appended to the chapters. There is a good index, and the publishing is excellent. The set should be in all medical libraries and in the collections of orthopedists.

Smoking and Cancer: A doctor's report. By Alton Ochsner, M.D. 8°, cloth, 86 pp., with illustrations. New York: Julian Messner, Incorporated, 1954. $2.00.

Dr. Ochsner, former president of the American Cancer Society and the American College of Surgeons, is well qualified to write this popular book on the smoking problem. He analyzes the available statistics and information and concludes that there is a definite relation between smoking and respiratory and lung cancer. There is a bibliography of two pages and a good index. The book, although written for the laity, is recommended for all medical libraries.

Patologia del estomago operado. Segundo Congreso Argentino de Gastroenterologia, Mar del Plata, 13-18 de Abril, 1953. 8°, cloth, 482 pp., with 124 illustrations. Buenos Aires: Editorial Universitaria, 1954.

The complete session of this congress was devoted to gastric surgery in its various aspects. Lists of references

are appended to the chapters, and the publishing is good. The volume should be in all collections on gastroenterology.

Progress in Clinical Surgery. Edited by Rodney Smith, M.S., F.R.C.S., surgeon, St. George's Hospital, London. 8°, cloth, 414 pp., with 112 illustrations. Boston: Little, Brown and Company, 1954. $7.50.

This symposium is the joint work of 20 British surgeons, who write on 30 subjects of surgical interest. Lists of references are appended to the articles; the printing was done in Great Britain. This semiserial should be in surgical collections.

NOTICES

LIFE INSURANCE MEDICAL RESEARCH FUND

The Life Insurance Medical Research Fund announces that applications for postdoctoral research fellowships (stipend, $3,600) will be accepted until October 15, 1955. Preference is given to those working on cardiovascular function and disease or related fundamental problems. Awards will be available July 1, 1956.

Applications for grants to institutions for aid in research on cardiovascular problems will be received until November 1, 1955. Support is available for physiologic, biochemical and other basic work broadly related to cardiovascular problems and also for clinical work in this field.

Further information may be obtained by writing to the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, New York.

INTERNATIONAL COLLEGE OF SURGEONS

The twentieth annual congress of the International College of Surgeons, United States and Canadian sections, will be held at Convention Hall, Philadelphia, September 12 through 15. Dr. George M. Piersol will preside at a symposium on blood derivatives and plasma substitutes. General assemblies will be held each morning and afternoon. Further information may be obtained by writing to Dr. L. J. Jackson, United States Chapter, 1516 Lake Shore Drive, Chicago, Illinois.

AMERICAN COLLEGE OF CARDIOLOGY

The fourth interim meeting of The American College of Cardiology will be held at the Hotel Claridge, Memphis, Tennessee, November 10-12, 1955. Symposiums on rheumatic fever, rheumatic heart disease and vascular surgery will be featured. Further information may be obtained by writing to Dr. Phillip Reichart, Secretary, American College of Cardiology, Empire State Building, New York 1, New York.

NEW YORK MEDICAL COLLEGE CONFERENCE

A two-day conference on the practice of medical rehabilitation—home, office and hospital procedures—will be presented by the New York Medical College, Flower and Fifth Avenue Hospitals, October 27 and 28, 1955. Further information may be obtained by writing to Dr. Jerome S. Tobis, Director, New York Medical College, Flower and Fifth Avenue Hospitals, New York, New York.

BOSTON TUBERCULOSIS HOSPITAL

The twenty-ninth season of the South End Medical Club will open Tuesday, September 20, at noon. The first meeting will take place at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, Massachusetts. Dr. Franklin A. Neva will be the speaker. The subject will be "Consideration of Some Factors Relating to a Vaccine for Poliomyelitis." All physicians are invited to attend.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.
SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
SEPTEMBER 1. New England Health Institute. Page 1010, issue of June 9.
SEPTEMBER 1–28. Consultation Clinics for Crippled Children in Massachusetts. Page 391.
SEPTEMBER 12–21, DECEMBER 5–14, 1955, JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
SEPTEMBER 12–15. International College of Surgeons. Notice above.
SEPTEMBER 14–17. Heart-Disease Seminar. Page 260, issue of August 11.
SEPTEMBER 20. Boston Tuberculosis Association. Notice above.
SEPTEMBER 21. Essex North District Medical Society. Page 208, issue of August 4.
SEPTEMBER 21. New Jersey Neuro-Psychiatric Institute. Page 208, issue of August 4.
SEPTEMBER 26–30. Venereal-Disease Course. Page 348, issue of August 25.
SEPTEMBER 29–OCTOBER 1. Institute of Psychiatric Treatment. Page 302, issue of August 18.
SEPTEMBER 30–OCTOBER 1. American Medical Writers' Association. Page 118, issue of July 21.
OCTOBER 1 and 2 and 3–6. American Academy of Pediatrics. Page 118, issue of July 21.
OCTOBER 5. Arthritis and Rheumatism Foundation. Page 208, issue of August 4.
OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.
OCTOBER 10–21. New York Academy of Medicine. Graduate Fortnight. Page 84, issue of July 14.
OCTOBER 19 and DECEMBER 14, 1955 and FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 208, issue of August 4.
OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.
OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
OCTOBER 26 and NOVEMBER 30, 1955 and JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
OCTOBER 27 and 28. New York Medical College Conference. Notice above.
OCTOBER 27–29. Congress of Neurological Surgeons. Page 208, issue of August 4.
NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.
NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
NOVEMBER 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.
NOVEMBER 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.
NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.
NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
NOVEMBER 28–DECEMBER 2. Interim Session of the American Medical Association, Boston.
MARCH 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.
MAY 3–5, 1956. American Goiter Association. Page 348, issue of August 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 8

THURSDAY, SEPTEMBER 8
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Thoracic Conference. Circuit Grand Rounds. Drs. Hugh E. Wilson and Warren J. Taylor. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford, Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, SEPTEMBER 9
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

(Concluded on page xix)

Mysteclin

STECLIN-MYCOSTATIN
SQUIBB TETRACYCLINE-NYSTATIN

WELL TOLERATED BROAD SPECTRUM ANTIBACTERIAL THERAPY PLUS ANTIFUNGAL PROPHYLAXIS

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Because it contains Steclin (Squibb Tetracycline), MYSTECLIN is an effective therapeutic agent for most bacterial infections. When caused by tetracycline-susceptible organisms, the following infections are a few of those which can be expected to respond to MYSTECLIN therapy:

bronchitis	gonorrhea	osteomyelitis	pyelonephritis
colitis	lymphadenitis	otitis media	sinusitis
furunculosis	meningitis	pneumonia	tonsillitis

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BROAD SPECTRUM ANTIBIOTIC THERAPY, WITH A MINIMUM OF SIDE EFFECTS

In clinical use, Steclin has produced an extremely low incidence of the gastrointestinal distress sometimes observed with other broad spectrum antibiotics. Mycostatin (Squibb Nystatin), as contained in MYSTECLIN, is also a particularly well tolerated antibiotic and has produced no allergic reactions, even after prolonged administration.

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Because it contains Mycostatin, the first safe antifungal antibiotic, MYSTECLIN effectively prevents the overgrowth of Candida albicans (monilia) frequently associated with the administration of ordinary broad spectrum antibiotics. This overgrowth may sometimes cause gastrointestinal distress, anal pruritus, vaginitis, and thrush; on occasion, it may have serious and even fatal consequences.

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Each MYSTECLIN capsule contains 250 mg. Steclin Hydrochloride and 250,000 units Mycostatin.

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Supply: Bottles of 12 and 100.

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A well-balanced, high-potency vitamin formula containing B-Complex and C

FOLBESYN provides B-Complex factors (including folic acid and B_{12}) and ascorbic acid in a well balanced formula. It does not contain excessive amounts of any one factor.

FOLBESYN Parenteral may be administered intramuscularly, or it may be added to various hospital intravenous solutions. It is useful for preoperative and postoperative treatment and during convalescence.

Dosage: 2 cc. daily. Each 2 cc. provides:

Thiamine HCl (B_1)	10 mg.
Sodium Pantothenate	10 mg.
Niacinamide	50 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Ascorbic Acid (C)	300 mg.
Vitamin B_{12}	15 micrograms
Folic Acid	3 mg.

FOLBESYN is also available in tablet form, ideal for supplementing the parenteral dose.

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(Concluded from page 394)

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, SEPTEMBER 10
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, SEPTEMBER 12
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, SEPTEMBER 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, SEPTEMBER 14
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner, Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New Eng-England Deaconess Hospital.

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1. Weinberg, Arthur and Werner, W. E. F.: Bonadoxin, a new effective oral therapy for hyperemesis gravidarum. Am. Pract. and Dig. of Treatment. In press. 2. Personal communication. 3. Berenson, F.: Bonadoxin: oral therapy for nausea and vomiting of pregnancy. In press.

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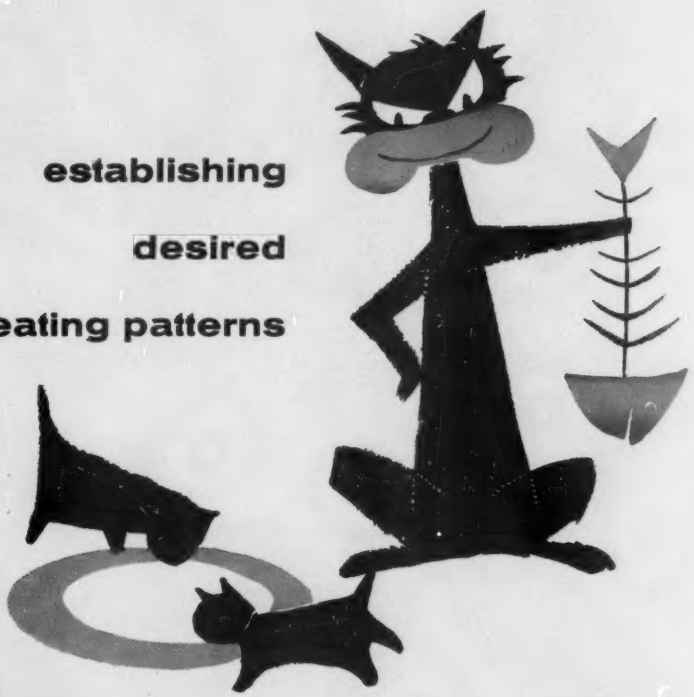

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1. Eisfelder, H. W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954.
2. Sebrell, W. H., Jr.: J.A.M.A., 152:42 (May) 1953.
3. Sherman, R. J., M.D.. Medical Times, 82:107 (Feb.) 1954

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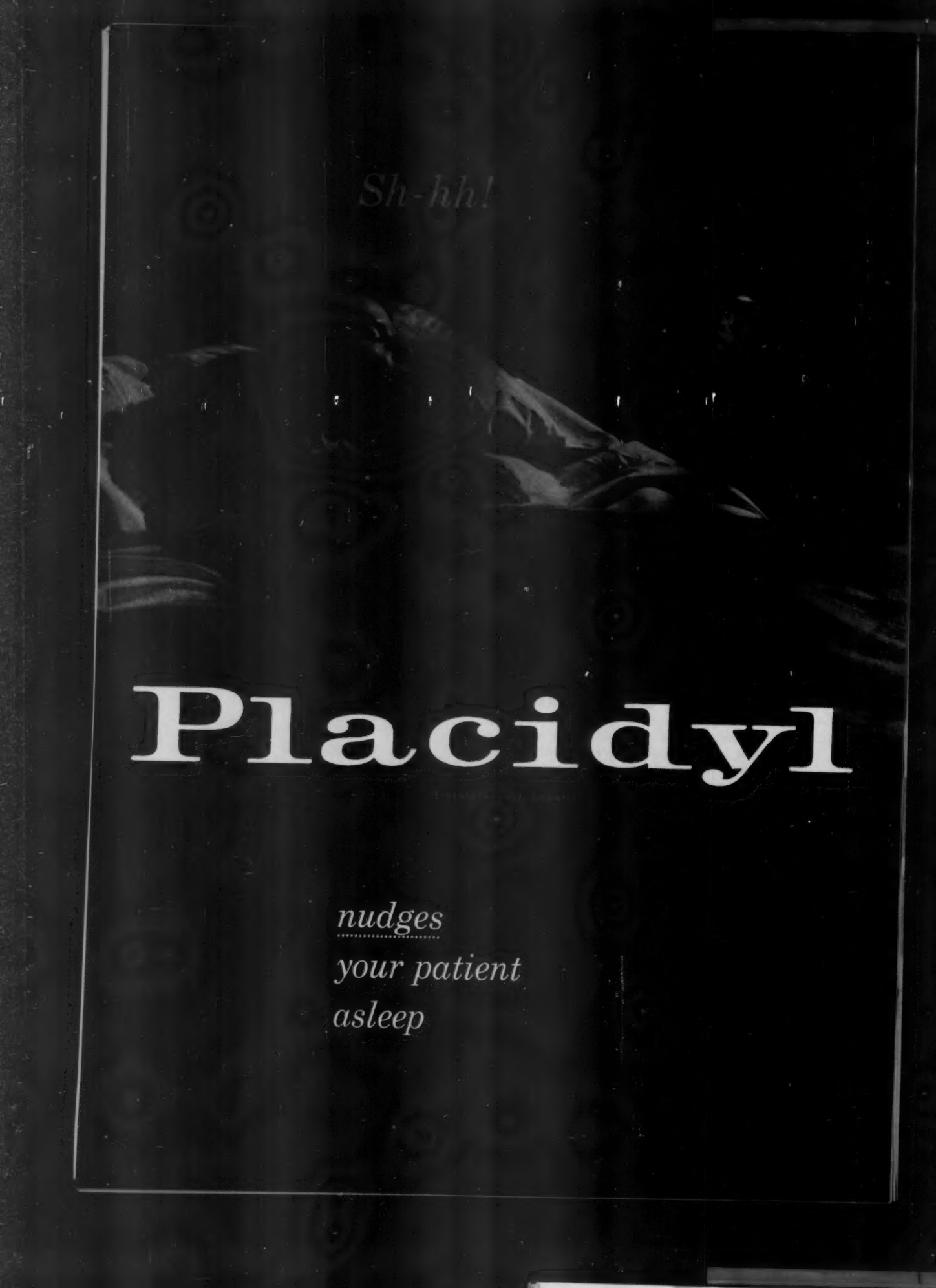
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Index to Advertisers

	PAGE
Abbott Laboratories	viii, ix, xxviii, xxix
American Hospital Supply Corp.	iii
Baldpate, Inc.	xxvi
Baxter Laboratories, Inc.	iii
Boston Medical Laboratory	xxiv
Ciba Pharmaceutical Products, Inc.	ii, xviii, xix
David Memorial Nursing Home	xxvi
Davies, Rose & Co., Ltd.	xi
Desitin Chemical Co.	v
Eaton Laboratories	x
Electroencephalographic Laboratory, Inc.	xxiv
Ethicon, Inc.	After vi
Fine Chemicals	iv
Foot-so-Port Shoe Company	xiv
Fuller Memorial Sanitarium	xxvi
Glenside, Inc.	xxvi
Hanover House, Inc.	xxvi
Hoffmann-La Roche, Inc.	After xiv
Irwin, Neisler & Company	vi
Lederle Laboratories	xiv, xviii, xx, xxi
Eli Lilly and Company	xvi
The S. E. Massengill Company	xxvii
The Medical Protective Co.	xxvi
Perkins School	xxvi
Riker Laboratories, Inc.	Back Cover
Ring Sanatorium	xxvi
A. H. Robins Co., Inc.	xv
J. B. Roerig Co.	xxv
W. B. Saunders Company	Front Cover
Schering Corporation	xiii
Sharp & Dohme (Div. of Merck & Co., Inc.)	xiv, xxii
Smith, Kline & French Laboratories	xii
E. R. Squibb & Sons (Division of Mathieson Chemical Corp.)	xvii
Storrow House (Massachusetts General Hospital)	xxvi
The Upjohn Co.	xxiii
Washingtonian Hospital	xxvi
Wiswall Sanatorium	xxvi
Woodside Cottages, Inc.	xxvi

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